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METASTATIC TUMORS OF THE BRAIN

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The literature is rich in valuable information on the anatomy and clinical manifestations of primary tumors of the brain. It is rather poor in its yield of similar data in relation to metastatic tumors of the brain. Yet the latter are not rare, as shown by several reliable statistical studies in which the occurrence of metastatic tumors as compared with that of other expanding intracranial lesions is considered. Thus, in the Cushing analysis of 2,000 verified brain tumors [1] the metastatic neoplasms of the brain constituted 4.2 per cent. Walshe [2] gave a somewhat higher incidence of metastatic tumors of the brain, his figures being 6.4 and 7.7 per cent for carcinoma and sarcoma, respectively, in a total of 642 cases of brain tumor. Dandy [3] gave 10 per cent as a rather rough estimate of the incidence of metastatic neoplasms among tumors of the brain of all varieties. Adson,[4] on the other hand, reported only 2 cases of metastatic carcinoma in a group of 167 brain tumors. In contrast to all these statistics, our own series of the metastatic tumors constitutes about 13.5 per cent of the entire collection of brain tumors encountered at necropsy at the Mount Sinai Hospital. This higher incidence finds a probable explanation in the fact that our material is drawn not only

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1. Cushing, H.: Intracranial Tumors: Notes on a Series of Two Thousand Cases, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

2. Walshe, F. M. R.: Intracranial Tumors: A Critical Review, Quart. J. Med. **24**:587, 1931.

3. Dandy, W.: Metastatic Tumors, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 669.

4. Adson, A. W.: The Surgical Consideration of Brain Tumors, Quart. Bull. Northwestern Univ. M. School **35**:1, 1934.

from the neurologic and neurosurgical services but from the division of medicine and general surgery.

Despite this discrepancy in the statistical data, it is obvious that metastatic tumors of the brain deserve greater interest than has heretofore been accorded them. A closer study of this apparently frequent form of expanding cerebral lesion is invited also by the observation that it often presents a difficult diagnostic problem. Such is the case when a metastatic tumor is single, and then almost indistinguishable from one that is primary in the brain, or when the lesion, being multiple and asymmetric in distribution, leads the examiner astray by exhibiting signs and symptoms simulating those of vascular or inflammatory disease of the brain. On the other hand, with the expanding character of a single lesion already recognized and its location determined, the neurologist is occasionally confronted by another, no less difficult, problem—that of the advisability of surgical intervention.

As in the case of primary neoplasms of the brain, a satisfactory solution of the diagnostic problems presented by the metastatic tumors demands a better understanding of the anatomic and clinical behavior of such lesions. To that end the following analysis of a relatively large series of cases (57) of clinically carefully observed and anatomically verified metastatic tumors of the brain was undertaken. For purposes of a more comprehensive presentation of the clinical records, it was found advisable to classify the cases as follows:[5]

Group 1: Cases in which the existence of a brain tumor was only suspected and remained in doubt until late in the clinical course.

Group 2: Cases in which an expanding lesion was seriously considered, its neoplastic character remaining in doubt.

Group 3: Cases in which the neoplastic character of the brain tumor was recognized but its metastatic nature was not suspected.

Group 4: Cases in which the presence of a cerebral neoplasm of metastatic origin was recognized but no detectable primary focus was found, although circumstantial evidence pointed to its existence.

Group 5: Cases in which the metastatic character of the intracranial expanding lesion was recognized and its primary source looked for and found in some instances, while in other instances only other sites of metastasis were detected.

Group 6: Cases in which the cerebral manifestations appeared as a terminal event late in the clinical course or cerebral metastasis was discovered only at necropsy.

REPORT OF CASES

GROUP 1.—*Existence of tumor in doubt or not suspected until late in the clinical course* (9 cases).—In most of the cases in this group

5. Globus, J. H., and Selinsky, H.: Metastatic Tumors of the Brain, Arch. Neurol. & Psychiat. **17**:481 (April) 1927.

a diagnosis of some disorder of the central nervous system other than tumor of the brain was made during the early part of the clinical course. Only when some more definite evidence of increased intracranial tension made its appearance, along with more localizing neurologic changes, was the suspicion of an expanding intracranial lesion aroused. Thus, in 3 cases the diagnosis of virus meningoencephalitis was made, while the possibility of syphilitic meningoencephalitis was considered in 2 cases. A diagnosis of cerebral thrombosis was made in 3 cases, and the presence of a psychoneurosis was seriously considered in 1 case until late in the clinical course. Cases 1 to 6 were selected to illustrate some of the clinical manifestations which obscured the true anatomic character of the cerebral involvement.

CASE 1.—*Sudden onset during an epidemic of encephalitis of cerebral manifestations of three weeks' duration. Disseminated neurologic signs, with evidence of increased intracranial pressure. History of previous removal of a malignant tumor of the leg. The possibility of metastatic tumor was considered, but partial recovery and other considerations led to the diagnosis of encephalitis. Sudden death, believed to be due to intraventricular hemorrhage. Necropsy: hemorrhagic mass in the lateral ventricle, later recognized as melanoblastoma.*

History.—B. G., an actress aged 21, three years before admission to the hospital had a pigmented mole removed from her leg. It was diagnosed as a melanosarcoma; three weeks later the inguinal glands became enlarged; they were found to be infiltrated and were excised. She remained apparently well until five weeks before admission to the hospital (April 14, 1919), when she passed through an attack of bronchitis, making an uneventful recovery. Two weeks later she suddenly vomited; there was a slight rise in temperature, and shortly thereafter she became stuporous. She remained in this condition for two days, then recovered and was again well enough to be up and about for the next ten days. During that time she felt somewhat drowsy and complained of headache, pain behind the eyes, inability to look at a bright light and, occasionally, double vision. The headaches grew in intensity; she vomited frequently and gradually became confused. Her temperature rose slightly.

Examination.—The significant findings included bilateral ptosis, greater on the left side than on the right; weakness of the left external and internal rectus muscles; bilateral papilledema with retinal hemorrhages; deviation of the tongue to the right; bilateral weakness of the face, more marked on the left side; depressed deep reflexes of the upper extremities; absence of knee reflexes, and an active achilles reflex. The patient was somewhat disoriented and euphoric.

Laboratory Data.—The Wassermann reaction of the blood was negative, and the roentgenogram of the skull revealed nothing abnormal. A lumbar puncture yielded xanthochromic fluid under increased pressure, containing 8 cells per cubic millimeter. The blood pressure was 110 systolic and 77 diastolic.

Course.—The diagnosis at first rested between metastatic tumor of the brain and acute epidemic encephalitis. The initial improvement with disappearance of the drowsiness and reduction in the diplopia strengthened the belief that the case was one of encephalitis. A decline in the patient's condition soon followed, and new objective signs appeared, such as exophthalmos on the right, jerky movements of both hands, more pronounced on the left side, weakness of the right hand grip and disjointed, independent movements of both eyes. The diagnosis of a

cerebral tumor now came to the fore, and operation was seriously considered, although localization was difficult. Another lumbar puncture showed xanthochromic fluid. Another short remission was followed by a rapid decline, death occurring suddenly after the patient had swallowed a small amount of ammonia water by mistake.

Necropsy (examination limited to cranium).—Gross Anatomic Changes: The brain showed slight flattening of the convolutions. On section, a large red mass, not unlike a clot of blood, was observed in the body of the left lateral ventricle. It was about the size of a hen's egg, showed evidence of organization (fig. 1) and closed the left foramen of Monro. The walls of the ventricle showed dark

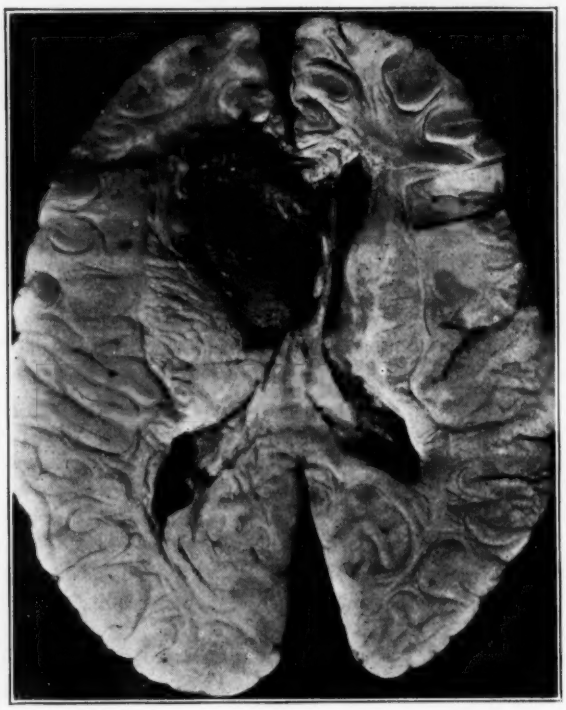

Fig. 1 (case 1).—Horizontal section of the brain, showing the melanoblastoma in the lateral ventricle (the microscopic appearance of the tumor was like that in case 17, figure 11 *B*).

discoloration. This discoloration also had affected the thalamus and the caudate nucleus on the same side. A small area about the size of a pea, suggesting a subcortical hemorrhage, was noted in the posterior end of the second temporal convolution.

Microscopic Observations: Histologic study of the so-called blood clot revealed a massive collection of pigmented cells. The dominant cell form was large and round, with a large vesicular nucleus. Most of these cells contained coarse, brown or black granules, evenly distributed throughout the cytoplasm (see case 17, fig. 11 *B*). The cells displayed no particular arrangement, although in places there was

a tendency to gather about blood vessels. Here and there were islands of red blood corpuscles, and interspersed among the neoplastic cells were some polymorphonuclear leukocytes and a thin connective tissue stroma.

The acute onset during an epidemic of acute encephalitis of an illness characterized by irregularity in the clinical course and disseminated objective manifestations associated with periods of lethargy justified in this case the suspicion of an inflammatory disease of the brain. However, serious consideration was given to metastasis to the brain in view of the previous removal of a malignant neoplasm.

It is interesting, too, to note that the postmortem diagnosis was also at first encephalitis and that the intraventricular mass was regarded as a hemorrhage. Several years later a thorough study of this mass led to the discovery that the so-called organized hematoma was a metastatic melanoblastoma.

The intraventricular location of the tumor fully explains the frequent variations in the clinical picture, as well as the severe internal hydrocephalus with resultant papilledema, the xanthochromic discoloration of the cerebrospinal fluid and the stormy character of the clinical course.

CASE 2.—*Acute onset of cerebral manifestations of four weeks' duration: headache, vomiting and vertigo. Disseminated signs of cerebral and meningitic involvement. Rapid decline and death. Necropsy: multiple metastatic carcinoma (primary in the left bronchus), with a nodule in the fourth ventricle.*

History.—T. B., a woman aged 52, was admitted to the hospital on March 31, 1923, with the complaint of headache and vomiting of four weeks' duration. She had had influenza four years previously and had passed through the menopause at the age of 50. The fatal illness was abrupt in onset and began with severe headache, repeated vomiting and pain in the abdomen. The headaches, limited chiefly to the left frontoparietal region, became constant and grew in severity, while the epigastric pain became less constant. The vomiting continued and was not related to meals; it was usually preceded by a great deal of retching and was frequently precipitated by sudden movement of the head. The vomitus contained occult blood.

Examination.—The patient was poorly nourished and appeared chronically ill. She was somewhat drowsy, and there was an acetone odor to the breath. Rigidity of the neck, bilateral Kernig and Brudzinski signs, blurring of the nasal halves of the disks, right hemiparesis with increased deep reflexes on that side, absence of abdominal reflexes and a positive Babinski sign on the right were the essential neurologic findings. The patient was incontinent of urine and feces.

Laboratory Data.—A lumbar puncture yielded clear cerebrospinal fluid under moderately increased pressure, containing 100 lymphocytes per cubic millimeter. The Wassermann reactions of the blood and cerebrospinal fluid were negative; the colloidal gold curve of the cerebrospinal fluid was normal. The blood pressure was 120 systolic and 90 diastolic.

Course.—The patient's first week in the hospital was marked by the development of slight ptosis on the right side, reduction in the pupillary reaction to light and mild hypalgesia of the right side of the body. The case was considered one of epidemic meningoencephalitis, while a cerebral neoplasm was regarded only

as a remote possibility. Soon, however, additional symptoms appeared, such as paralysis of upward gaze, weakness of the right internal rectus muscle with poor convergence and tenderness on percussion over the left side of the skull. The diagnosis of meningoencephalitis was still regarded as most probable. The cell count of the cerebrospinal fluid obtained by a second lumbar puncture was 128 lymphocytes per cubic millimeter. At the end of two weeks in the hospital she

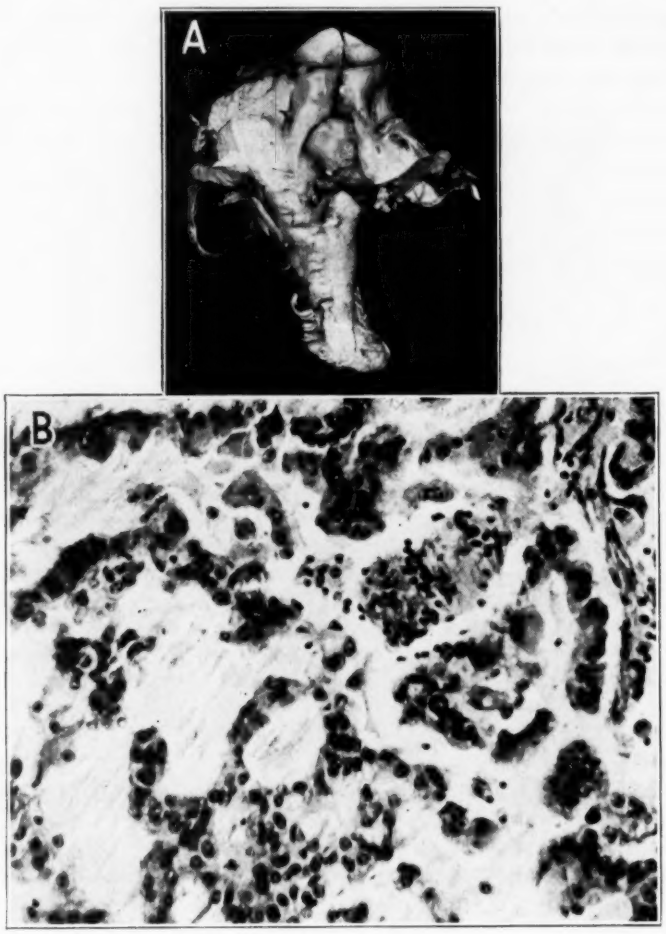

Fig. 2 (case 2).—*A*, gross appearance of the small metastatic nodule in the floor of the fourth ventricle.

B, histologic character of the metastatic nodule. × 240.

displayed more definite evidence of involvement of the third nerve, such as ptosis of the right upper eyelid, fixation of the pupil on the right side and paralysis of the internal and superior rectus muscles on the same side. The papilledema became more pronounced, and the larynx showed paralysis of the left abductor muscle. Gastric analysis revealed absence of free hydrochloric acid and a total

acidity of 30 degrees. In view of the values for gastric acidity and the increasing papilledema, the possibility of a metastatic neoplasm came under consideration. A third lumbar puncture yielded clear cerebrospinal fluid, containing 60 lymphocytes per cubic millimeter. The condition of the patient declined rapidly, and she died on the twenty-fifth day in the hospital.

Necropsy.—Gross Anatomic Changes: There was no decided evidence of increased intracranial pressure. On section of the brain, a few small yellowish areas, measuring about 1 cm. in diameter, were seen scattered through the left frontal lobe. They were sharply demarcated from the surrounding brain tissue. The ventricles appeared dilated. Sections of the cerebellum revealed a yellowish mass, measuring 2 by 3 cm., situated in the white substance of the right lobe. A spherical tumor about 1.5 cm. in diameter, springing by a narrow pedicle from its floor, was observed in the fourth ventricle (fig. 2 *A*).

Microscopic Observations: Sections of the several tumor masses showed them to be metastatic lesions. The histologic character of the tumors was identical with that of the primary growth in the lung. The tumor tissue was made up of numerous alveoli lined by cuboidal epithelium and filled with mucous material (fig. 2 *B*). The alveoli were separated from each other by a vascular connective tissue stroma.

General Necropsy Observations.—Primary carcinoma was present in the left upper bronchus.

The precipitate onset, the dissemination of the clinical features, the meningeal signs and the pleocytosis justified the diagnosis of meningoencephalitis. However, the intense headache, the Bruns syndrome (marked vertigo on active movement of the head), the tenderness to percussion and the suggestive results of gastric analysis were of sufficient significance to arouse more than a suspicion of metastatic tumor of the brain. Under such circumstances the primary lesion would be placed in the gastrointestinal tract, but postmortem examination recalled that no tumor was present here and that the primary lesion was in the lung.

CASE 3.—*Cerebral symptoms of six months' duration, preceded by pulmonary signs of five years' duration. Disseminated neurologic signs, including those of meningeal involvement. Terminal psychosis. Rapid decline. Death, without operation. Necropsy: metastatic carcinomatosis of the brain and meninges.*

History.—F. M., a salesman aged 44, married, entered the hospital on Oct. 13, 1924. An occasional attack of dyspnea on slight exertion, weakness and palpitation, associated with a mild but persistent cough, without hemoptysis or night sweats, marked the five years preceding the onset of the fatal disturbance. The illness began six months prior to his admission to the hospital with the appearance of an annoying noise in the head and ears and general malaise, accompanied by loss of weight. Four months later his voice suddenly became hoarse and in another five weeks his vision became impaired, while more recently he began to experience severe, knifelike pain between his shoulder blades. Shortly thereafter severe occipital headache, accompanied by attacks of dizziness, set in.

Examination.—The patient was in a poor condition, showing pronounced wasting and pulmonary signs, such as moist rales throughout the chest. The pupils were irregular and unequal, the left being fixed to light, while the right eyelid was ptosed. Weakness of the left side of the face and slight paresis of the

left arm were present. Some impairment of motion of the left side of the palate and a cadaveric position of the right vocal cord were noted on laryngoscopic examination. There were mixed deafness on the right side and total deafness on the left. The deep reflexes in the upper extremities were active and equal; the knee jerks were absent, and the abdominal reflexes were diminished. Roentgenographic examination of the chest revealed nothing abnormal. The colloidal gold test of the cerebrospinal fluid gave a curve characteristic of dementia paralytica. There were no abnormal masses or areas of tenderness in the chest or abdomen.

Course.—Meningoencephalitis, either syphilitic or tuberculous, was among the diagnostic possibilities considered; a diffuse neoplastic process was also postulated.

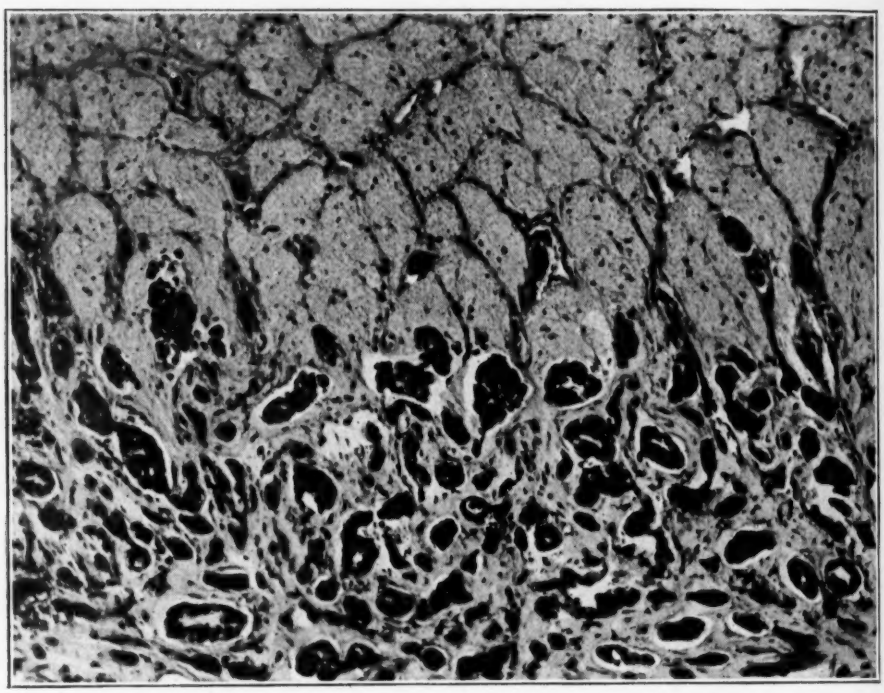

Fig. 3 (case 3).—Cross section of the optic nerve, showing its infiltration with carcinomatous (metastatic) cells along the meningeal extensions. × 105.

There was rapid decline, marked by intensification of the meningeal signs, increased rigidity of the neck, a more pronounced Kernig sign bilaterally and complete areflexia. Toward the end psychotic manifestations developed, and the patient died on the tenth day of his stay in the hospital.

Necropsy.—Gross Anatomic Changes: The left optic nerve showed a bulbous swelling extending from a point a little above the optic tract, which appeared to be invaded by a tumor; this mass was deep gray, firmer than the right nerve and measured from 5 to 6 mm. in diameter. A short distance to the left of this mass was another, a grayish white, firm tumor about 2 mm. in diameter. No other tumor could be seen anywhere over the surface of the brain or along any of the other cranial nerves.

The spinal cord showed a bulbous enlargement in the region of the ninth to the twelfth dorsal segment. Externally this portion of the cord was of normal color, but of slightly increased firmness. The meninges covering the spinal cord showed no gross pathologic alterations. The spinal nerves likewise were all grossly normal.

Microscopic Observations: Sections of the cerebral cortex with its meningeal coverings, the brain stem, the left optic nerve (fig. 3) and the spinal cord showed diffuse metastatic infiltration of the meninges and, in isolated areas, of the nerve tissue. The histologic appearance was that of an adenocarcinoma and was similar to that of the primary mass in the bronchus. The neoplastic cells formed acini and other groups, separated by a connective tissue stroma. The cells and their nuclei varied in size and shape, the cells tending to be columnar. Often two or more layers of cells lined the acini, and occasionally the cell outlines were so indistinct as to give the appearance of a syncytium.

General Necropsy Observations.—The diagnosis was primary adenocarcinoma in the right upper bronchus, with metastasis to the regional lymph nodes, the pericardium and the recurrent laryngeal nerve.

The tinnitus and the partial aphonia pointed to the implication of the eighth and tenth cranial nerves. These signs, when added to the meningeal manifestations, the radicular pain in the upper dorsal region and the loss of deep reflexes in the lower extremities, accompanied by symptoms of increased intracranial tension, such as headache and dizziness, pointed strongly to a meningeal process, disseminated in character, involving the brain, the spinal cord and the spinal roots. In addition, other signs of cerebral involvement, such as the paresis of the right arm, indicated that the process extended into the brain substance, justifying the diagnosis of a diffuse meningoencephalitic process. The repeated failure to find the tubercle bacilli spoke against a tuberculous origin, while the negative Wassermann reactions of the blood and the cerebrospinal fluid excluded syphilis as the causative factor. Thus, the diagnosis of a neoplastic process involving diffusely the meninges and the adjacent brain structure was accepted at the end of the clinical course. Such a diagnosis was in accord with the clinical course. The anatomic changes fully explained the clinical manifestations. However, the histologic picture was significant, indicating a much greater neoplastic involvement of the meninges than the gross appearance of the brain and its coverings suggested.

CASE 4.—*Cerebral symptoms of six months' duration. Generalized arteriosclerosis and lack of convincing evidence of increased intracranial tension. Amaurosis, questionable elevation of the disks and terminal psychosis. Necropsy: multiple metastatic carcinoma of the brain.*

History.—M. N., a married man aged 68, was apparently well until about six months before entering the hospital, on Dec. 15, 1923. At first there were brief episodes of dizziness; three months later impairment of vision set in, an ophthalmologic examination failing to reveal any apparent cause. Difficulty in swallowing, general weakness and insomnia followed. Shortly before admission to the hospital

he commenced to suffer from left-sided headache, displayed weakness of the right arm and leg and seemed to be completely blind. He soon became restless and irrational.

Examination.—There were signs of bilateral hypostatic pneumonia. Retinal arteriosclerosis, slight elevation of the disks and paresis of the right arm and leg were the main neurologic findings. A blood count showed slight leukocytosis; the urine was normal, and the blood pressure was 140 systolic and 110 diastolic.

Course.—The patient's decline was rapid; he became delirious and died on the fifth day in the hospital.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: In the left occipital lobe, 2 cm. anterior to the pole, an area about 3 cm. in its longest diameter was invaded by a growth. This mass was wedge shaped, with its apex directed toward and inserted into the depth of the brain substance, in

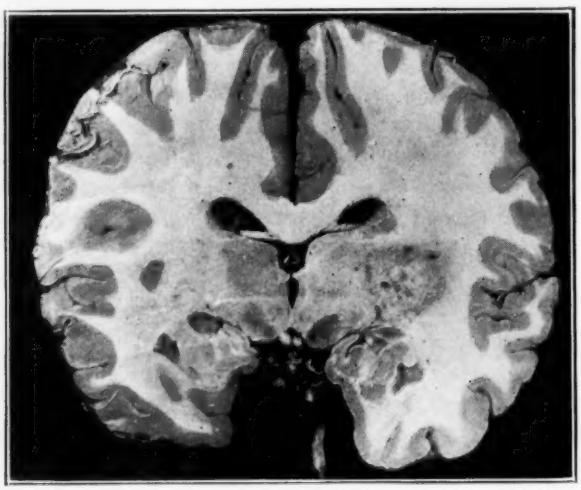

Fig. 4 (case 4).—Coronal section of the brain, showing a metastatic focus in one hemisphere. Another section somewhat caudad to the one illustrated showed a similar lesion in a similar location in the opposite hemisphere.

which it was embedded. The opposite occipital lobe in the corresponding location was flattened and on incision presented a mass similar to the one described, but more deeply located. The blood vessels at the base of the brain showed no pathologic alterations. On incision several small metastatic masses were also noted. A small rounded mass, about 1 cm. in diameter, was seen at the level of the genu of the corpus callosum, invading the cortex in the middle and inferior frontal convolutions on the left side. Adjacent to this mass were two cystic cavities; the subcortex around and adjacent to the mass was edematous and swollen. Another mass was observed in the subcortex on the left side adjacent to the corpus callosum just above the formation of the internal capsule, at a point at which the striatum was broken up into its constituent parts. Roughly at the level of the middle portion of the island of Reil, another large mass, about 2 cm. in diameter, was found in the subcortex, invading the internal capsule and partially involving the thalamus. At the level of the posterior third of the

island of Reil two small areas were observed, the one on the left side being larger than the one on the right; these masses were adjacent to the surface of the brain and were brownish red, with a pinkish white center (fig. 4).

Microscopic Observations: Section showed the tumor masses to be made up of alveoli lined by cuboidal and low columnar epithelium, some of the alveoli containing colloidal material. Irregularly interspersed in the tumor were areas of necrotic material and zones of connective tissue, in which ramified many blood vessels. The condition was diagnosed as metastatic adenocarcinoma, primary in the prostate.

The presence of arteriosclerotic neuroretinitis favored the diagnosis of cerebral arteriosclerosis with areas of softening, in spite of the moderate blood pressure. The gross anatomic picture provided ample explanation for the general as well as the isolated clinical features. The bilateral involvement of the optic radiation may be considered as the cause of the amaurosis. The compression of the third ventricle by the large tumor mass resulted in hydrocephalus.

CASE 5.—*Cerebral manifestations of three months' duration in a patient who was known to have had a productive cough for two years. Moderately severe neurologic signs pointing to thrombosis of the left middle cerebral artery, of syphilitic or arteriosclerotic origin. Rapid decline; terminal bronchopneumonia. Necropsy: deep-seated metastatic tumor in the left cerebral hemisphere.*

History.—A man aged 65 began to experience difficulty in writing, attributed to weakness of the right hand, three months before admission to the hospital, on April 6, 1939. The weakness increased during the subsequent two months and spread to the right leg. Somewhat later speech became impaired, so that he was unable to find the desired words for expression. His history revealed that he had had a productive cough and dyspnea on exertion for two years and a 4 plus Wassermann reaction of the blood in 1937, at which time he was given antisyphilitic treatment.

Examination.—The patient was moderately euphoric but otherwise mentally normal. There was evidence of motor aphasia. The upper and lower extremities on the right side were weak and were held in the attitude of spastic hemiplegia. The pupils were slightly irregular but reacted well to light and in accommodation. On the right side the deep reflexes were hyperactive, the abdominal reflexes were absent and a Babinski sign was elicited. Vibratory sense was absent below the anterior iliac crest on both sides. The heart and lungs were normal. The blood pressure was 130 systolic and 70 diastolic.

Laboratory Data.—A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 60 mm. of water. There was only 1 lymphocyte per cubic millimeter. The total protein was 47 mg. per hundred cubic centimeters; the Wassermann reaction was negative, and the colloidal gold curve was normal. The Wassermann reaction of the blood was 4 plus. Chemical studies of the blood and urinalysis gave normal results.

Course.—It was felt that the clinical history and the objective signs pointed to the diagnosis of thrombosis of the left middle cerebral artery, with either

syphilis or arteriosclerosis as the causative factor. Antisyphilitic therapy was administered for four weeks, with but slight improvement. At the end of this period (May 9) the patient suddenly became disoriented and confused, the aphasia

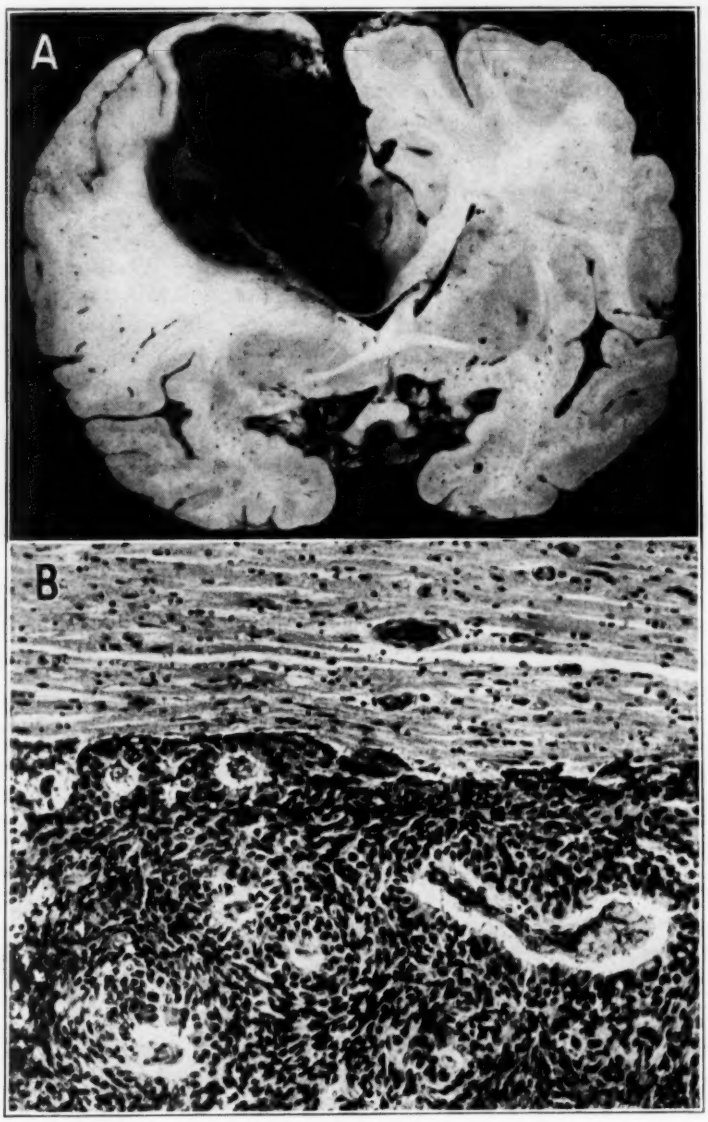

Fig. 5 (case 5).—*A*, gross appearance of the tumor, showing its rich vascular supply and sharp demarcation.

B, histologic character of the tumor. Here, again, the sharp delimination is well demonstrated. × 90.

became more pronounced and the hemiplegia became complete. Incontinence of urine and feces followed. The following six weeks were marked by a steady

decline and disorientation; bronchopneumonia developed and the patient died on June 21. At no time in the clinical course was a malignant growth with metastasis suspected.

Necropsy.—Gross Anatomic Changes: The convolutions of the left cerebral hemisphere were decidedly flattened, and there was an area of increased firmness in the posterior parietal area. A few arteriosclerotic plaques were noted in the basal vessels. Sectioning disclosed a large area of discoloration in the left cerebral hemisphere (fig. 5 *A*), extending from a point at the level of the genu of the corpus callosum as far back as the splenium. The area was situated near the mesial surface of the hemisphere, and in cross section its long axis ran parallel with the dorsal longitudinal fissure, being separated from the latter by a layer of cortex. The lower pole of the mass rested on the corpus callosum, which was invaded; its upper pole extended to within about 0.5 cm. of the dorsal border of the hemisphere. This area of discoloration was delimited from the adjacent tissue by a well defined margin of pearly white tumor tissue. The mass was somewhat lobulated, presenting two main parts. At the periphery it showed a small island of hemorrhagic material, again well delimited from the adjacent tissue.

Microscopic Observations: The tumor mass (fig. 5 *B*) consisted of numerous islands of neoplastic cells, irregularly separated from one another by wide zones of extravasated blood. Throughout the tumor there were trabeculae of connective tissue, containing many blood vessels. Thin-walled blood vessels were observed in the center of the islands of neoplastic tissue, the cells of which exhibited a variety of forms. Those nearest the blood vessels were somewhat cuboidal, while those farther away were oval and tended to form streams of parallel cells. The nuclei were similar in shape to their cells and were for the most part vesicular. Mitotic figures were seen. The large area of extravasation within and adjacent to the tumor contained many macrophages with coarse, pigmented granules in their cytoplasm. The cerebral substance adjacent to the tumor showed rarefaction of tissue, vascular congestion, increase in glial nuclei and moderate degenerative alterations in the nerve cells.

General Necropsy Diagnosis.—The diagnosis was carcinoma, primary in the upper lobe of the left lung.

The rather acute onset of symptoms and signs pointing to a discrete lesion in the left hemisphere in a patient of advanced years who was known to have had a positive Wassermann reaction of the blood justified the original diagnosis of a vascular process in the brain, either of syphilitic or of arteriosclerotic origin. In retrospect, it may be said the productive cough and dyspnea on exertion should have put one on guard and have aroused the suspicion of a probable malignant process in the lungs. Roentgenographic examination of the chest probably would have established the diagnosis.

CASE 6.—*Amputation of the right breast four years prior to the development of signs of neurologic disorder, which began with lumbosacral root pain, followed by severe anorexia, diagnosed as anorexia nervosa. Pronounced psychic manifestations. Terminal development of papilledema; rapid decline; bronchopneumonia; death. Necropsy: multiple metastatic carcinoma of the cerebellum.*

History.—A woman aged 30 entered the hospital on March 5, 1939, complaining of "sciatic pain" and pronounced anorexia. Four years earlier (January 1935)

she had undergone radical amputation of the right breast for a scirrhous carcinoma. She remained in apparently good health until August 1938, when she began to experience pain in the lower portion of the back, radiating to both thighs. She was told that she was suffering from "sciatica" caused by exposure to cold. The pain persisted and spread to the head and neck. She entered a hospital early in February 1939; there roentgenographic examinations of the spine, pelvis, chest and skull failed to reveal anything abnormal, and the results of a lumbar puncture were also reported as without significance. In the meantime the anorexia became more pronounced, and by the middle of February she could not retain solid food. At this time she entered the Mount Sinai Hospital.

Examination.—The patient was emaciated, weighing only 80 pounds (36.3 Kg.). The neurologic signs were meager; the pupils reacted sluggishly to light and in accommodation; the left eye was frequently held closed; the deep reflexes were hyperactive. Mentally she appeared to be intact, being oriented in all fields, but emotionally she manifested pronounced instability. She was uncooperative, at times melodramatic, often smiled without apparent cause and expressed bizarre ideas.

Laboratory Data.—A lumbar puncture yielded clear, colorless cerebrospinal fluid under an initial pressure of 90 mm. of water. The total protein was 102 mg. per hundred cubic centimeters. The basal metabolic rate varied from -10 to $+10$ per cent. A Janney test showed a high sugar curve, with a maximum of 200 mg. per hundred cubic centimeters at the three hour interval. Roentgenographic investigation of the gastrointestinal tract revealed nothing significant.

Course.—In view of the lack of localizing neurologic signs and the presence of a severe emotional conflict, known to have been due to difficulties in her marital life, psychoneurosis with a severe form of anorexia nervosa was considered as a probable diagnosis. She was placed on a special diet and given vitamin B complex, without beneficial results. During the third week in the hospital nystagmoid jerks on lateral and upward gaze and papilledema of 0.5 D. in the left disk were noted for the first time. These and the vegetative disturbances led to the suspicion of an expanding lesion in the diencephalon. On encephalographic examination (April 4) no air entered the ventricular system; a small collection of air was noted in the supracallosal sulcus and over the cerebral cortex. The skull itself and the lumbosacral region, as well as the pelvis, appeared normal on roentgen examination, but the roentgenograms of the chest revealed two nodules, one in each lung, each measuring about 1½ inches (3.8 cm.) in diameter. They were considered to be metastatic. In the course of the next few days a rapid advance of the papilledema in the left eye took place and retinal hemorrhages appeared. The right eye remained free of changes. A steady decline followed; the headaches became more severe and mental changes more pronounced. Suddenly, on April 18, her temperature rose; signs of terminal bronchopneumonia appeared, and she died on April 22.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: On sectioning the brain, bilaterally symmetric internal hydrocephalus, affecting the lateral as well as the third and fourth ventricles and the iter, was noted. The fourth ventricle was somewhat deformed and displaced to the right. A tumor, measuring 5 cm. in the horizontal and 3.5 cm. in the vertical plane, was observed in the left cerebral lobe (fig. 6). It occupied almost the entire lobe, there remaining but a thin rim of cerebellar tissue about the tumor. The latter was well demarcated from the adjacent structures. The center of the tumor was occupied by a large mass of gelatinous material. On tracing this mass posteriorly it was

found to diminish in circumference. At its dorsal aspect and within the cerebellar cortex there was another small, solid tumor mass, measuring about 1 cm. in diameter. A similar lesion was seen in the right middle cerebellar peduncle.

Microscopic Observations: Sections of the tumor in the cerebellum stained with hematoxylin and eosin showed the presence of irregular areas of neoplastic cells interspersed with varying amounts of connective tissue. The tumor cells varied in size and shape and in the relative density of chromatin material. Occasionally one saw a clumping together of many cells, giving the appearance of multinucleated giant cells. Areas of necrotic tissue were present, along with

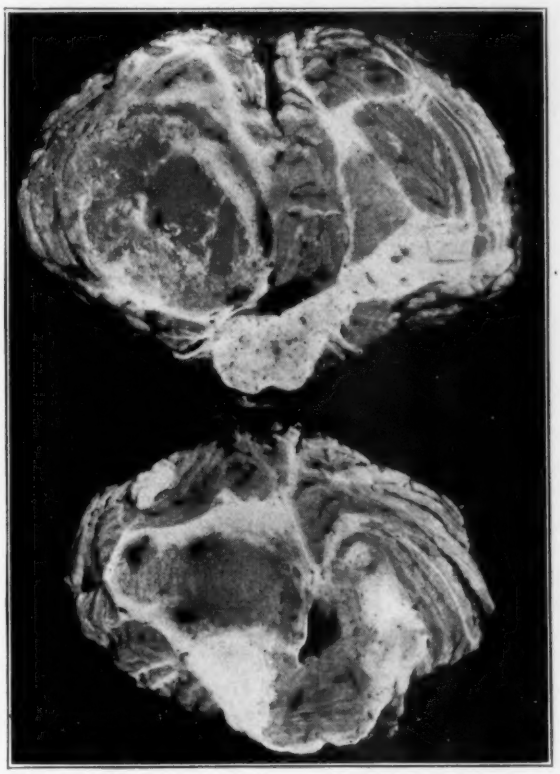

Fig. 6 (case 6).—Gross appearance of the tumors. Note the gelatinous cyst in the upper section and the multiplicity of the lesions in the low section.

hemorrhages. Throughout the connective tissue stroma there were many thin-walled blood vessels. The tumor was fairly well demarcated from the surrounding tissue, but in the substance immediately adjacent could be seen small groups of neoplastic cells.

Attention may be drawn to the paucity of the objective neurologic signs in the early part of the clinical course in this case. The history of a primary malignant growth elsewhere, in the breast in this case, should, however, have aroused a strong suspicion of the probable

existence of a metastatic focus in the brain. Highly significant was the finding on roentgenographic examination of metastatic nodules in the lung, a lesion one should look for in any instance of a suspected metastatic tumor in the brain.

GROUP 2: *Presence of an expanding lesion seriously considered, its neoplastic character remaining in doubt* (5 cases).—In this group, as illustrated by cases 7 and 8, the failure to recognize the neoplastic character of the lesion was due to the rather abrupt onset of symptoms, unassociated with any other systemic disorder, to the short clinical course and to a history of trauma in several cases.

CASE 7.—*Acute onset of a fragmentary jacksonian sensory attack, followed by left hemiparesis, left-sided signs of involvement of the pyramidal tract and sensory disturbances of the left side. Craniotomy; no tumor revealed. Gradual decline. Necropsy: metastatic carcinoma in the right parietal lobe.*

History.—A man aged 40 was apparently well until nine months before entry to the hospital, on Oct. 28, 1930, when he suddenly experienced a momentary feeling of "electricity" and numbness radiating from the toes to the hip on the left side. Shortly thereafter he became subject to occasional mild attacks of dizziness, pain on the right side of the head and moderate anorexia. One week after the onset of the illness he passed through another episode of a feeling of "electricity" in both legs, and in another week numbness suddenly developed in the left arm and left leg, which was accompanied by a fall to the floor, without loss of consciousness. The impairment in sensation, a feeling of heaviness and partial loss of power in the left arm and leg became constant; there was also some loss of weight.

Examination.—The pupils were small and irregular. The left palpebral fissure was wider than the right; the optic nerve heads were slightly elevated, and their margins were indistinct. The deep reflexes were exaggerated on the left side, and the abdominal reflexes on the same side were much depressed. Ankle clonus was present on the left side, and at times there was a suggestion of a Babinski sign on the same side. Marked diminution of sensation in all modalities was present on the left side.

Laboratory Data.—The cerebrospinal fluid was clear, with an initial pressure of 140 mm. of water. All laboratory examinations of the cerebrospinal fluid, including the Wassermann and colloidal gold tests, gave normal results. There was no record of a roentgenographic examination of the chest. Studies of the blood and urine gave normal results.

Course.—The presence of a tumor deep in the right cerebral hemisphere was considered. Encephalographic examination, carried out one week after admission, revealed a shift of the entire ventricular system to the left, with moderate dilatation of the left and distortion of the right lateral ventricle. Subarachnoid markings were absent in the right frontoparietal region. A craniotomy, performed on November 10, revealed no tumor. After the operation the patient remained in a state of semistupor; his condition declined gradually, and he died eleven days after the craniotomy.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: The brain was under slightly increased pressure. A tumor occupied the entire right superior parietal lobule (fig. 7*A*). Anterior and ventral to the tumor was a wide

zone of softening. On sectioning the brain, the tumor was seen to be well circumscribed and restricted to the right parietal region. It measured 2.5 cm. in width and 3 cm. in vertical diameter. It was gray and granular and had a few small

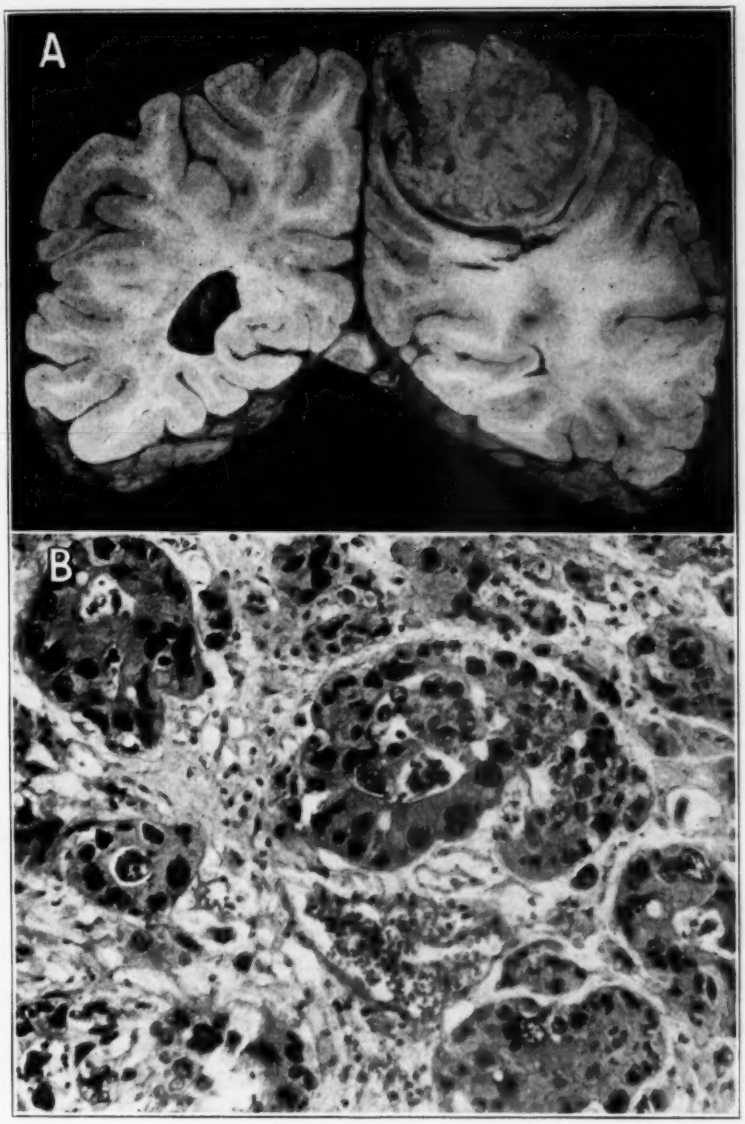

Fig. 7 (case 7).—*A*, coronal section of the brain, showing the gross character and location of the metastatic tumor.

B, histologic character of the tumor. × 170.

hemorrhagic areas at its periphery. The tumor was clearly demarcated from the uninvolved brain substance and had penetrated the subcortical white matter. It

extended anteriorly to a point about 1 cm. in front of the splenium of the corpus callosum and posteriorly as far back as 0.5 cm. in front of the parieto-occipital fissure. At the lower edge of the tumor there was an area of softening.

Microscopic Observations: The tumor was for the most part necrotic. Between the necrotic tissue and the brain substance was a zone of tumor tissue. This consisted of numerous islands of neoplastic cells, separated from one another by thin walls of connective tissue, in which ramified a moderate number of capillaries. Some of the islands of neoplastic tissue contained in part cells arranged in a single layer enclosing a small central space, the structure resembling a well formed acinus (fig. 7 *B*). Their nuclei were vesicular or heavily chromatinized and were situated at the base of the cells. There was a relatively large amount of cytoplasm. In other islands were large numbers of cells varying in shape and size, with nuclei heavily chromatinized or vesicular and situated at almost any part of the cell. Some nuclei appeared to have fused with one another, forming large, irregular, chromatinized masses. The neoplastic tissue was well demarcated from the adjacent brain substance, but the latter reacted with an increase of glia cells, including the ameboid form, congestion of blood vessels and slight degenerative changes in neighboring nerve cells.

In cases of primary tumor of the brain the unfolding of the clinical picture may be so rapid as to suggest an acute process. In such instances it is often impossible to do more than suspect the existence of a cerebral tumor. Under such circumstances the metastasizing character will escape recognition, particularly when other diagnostic leads are not available. The secondary nature of the metastatic lesions will seldom be suspected when the focalizing signs are discrete.

Case 8.—*Violent injury to the head, followed by loss of consciousness for one-half hour and later by headaches, visual impairment, confusion, impairment of memory and difficulty in walking. Papilledema, left hemianopia, left-sided signs of involvement of the pyramidal tract and sensory impairment on the left side. Subdural hematoma or neoplasm in the temporal lobe was considered. Craniotomy; no tumor revealed. Stupor and terminal bronchopneumonia. Necropsy: metastatic adenocarcinoma in the right parieto-occipital lobe.*

History.—A man aged 53 entered the hospital on Dec. 8, 1936. He had been apparently well until four months prior to the date of admission, when he met with an unusual accident. A man falling from a height of 20 feet (6 meters) struck the patient's head, knocked him down and rendered him unconscious for about thirty minutes. For more than a week thereafter he had persistent headache. He returned to his job three days after the accident but was unable to work as rapidly as before. Shortly thereafter he began to be troubled with blurred vision; he complained of seeing "colored fire spots," and reading caused headache. Two months later he became aware of impairment of memory and of confusion. He also began to experience increasing difficulty in walking. His disabilities increased, and there was progressive loss of weight.

Examination.—The pupils were unequal, the left being larger than the right. Some impairment of movement of the right external rectus muscle was demonstrated. There was left homonymous hemianopia. Papilledema was present bilaterally. There was slight weakness of the left side of the face of the mimetic type. Some weakness of the left hand grip was noted. The patellar reflex was exaggerated; the abdominal reflexes were absent on the left side; there were poor

flexion to plantar stimulation and an Oppenheim sign on the left side, and ankle clonus was elicited on both sides. Position, vibratory and tactile senses were diminished on the left side. On walking the left arm swung poorly, and the patient tended to limp with the left leg. He displayed some euphoria and perseveration. There was moderate tenderness in the left occipital and the right temporo-occipital region of the skull. He was emaciated. The blood pressure was 145 systolic and 80 diastolic. Examination of the lungs showed some impairment of resonance at the apex of the right lung.

Laboratory Data.—A lumbar puncture yielded clear, colorless cerebrospinal fluid, containing 3 monocytes per cubic millimeter. The Pandy reaction was 3 plus. The Wassermann reaction was negative, and the colloidal gold curve was normal. The Wassermann reaction of the blood was negative, and routine examinations of the blood and urine gave normal results. A roentgenogram of the skull showed no fracture.

Course.—In view of the history of trauma to the head, a subdural hematoma was seriously considered, but the possibility of a neoplasm was not entirely excluded. An exploratory craniotomy in the right frontoparietotemporal region was performed on December 14, but neither a hematoma nor a tumor was found. After this procedure the patient passed into stupor, and complete left hemiplegia developed. Bronchopneumonia set in, and he died on December 23, fourteen days after admission.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: Sectioning of the brain disclosed the right cerebral hemisphere to be larger than the left. There was some increase in consistency except in a small portion of the center of the right hemisphere. On tracing this area it was found to merge with a larger defect, which occupied the central portion of the parietal lobe and measured about 3 cm. in diameter. It contained a cavity nearly 1 cm. in diameter, surrounded by a wide zone of edematous tissue. Tracing it still farther backward, one encountered a hard, nodular mass which occupied almost the entire depth of the right occipital lobe and extended posteriorly to within 0.5 cm. of the occipital pole. The mass was well circumscribed, had a pearly white, granular appearance and was readily shelled out from the enclosing brain tissue. The lateral ventricles were displaced to the left. The left ventricle was larger than the right and was displaced upward. The right posterior horn was almost completely occluded by the tumor.

Microscopic Observations: A large portion of the tumor had undergone necrotic changes. Only at the periphery of the mass, particularly around the blood vessels, were intact cells present. There the cells had large, vesicular nuclei, varying considerably in size and shape. The tumor cells tended to arrange themselves in islands separated by a connective tissue stroma, in which ramified numerous blood vessels. Mitotic figures were frequent. In the proximity of the tumor the brain tissue showed considerable rarefaction, congestion of blood vessels and mobilization of compound granular ameboid glia cells.

The serious head trauma, followed immediately by the development of manifestations of intracranial involvement, justified the suspicion of subdural hematoma. Even the latent period preceding the development of focalizing signs supported such a diagnosis. The relation of the trauma to the development of the metastatic process in the brain will be discussed elsewhere in this article.

GROUP 3: *Diagnosis of intracranial tumor without the recognition, or even the suspicion, of its metastatic origin* (8 cases).—In the majority of the cases in this group the neurologic signs were of a character which indicated the presence of a single expanding lesion in the brain (case 9). In none of these did any signs or symptoms point to a possible primary seat of the malignant growth. In 1 instance (case 10) the multiplicity of lesions was quite evident, but their metastatic nature was not considered, for there were no readily detectable signs or symptoms pointing to a disorder in another organ nor was there anything to suggest a malignant process elsewhere. In another instance (case 11) even biopsy failed at first to aid in the identification of the true character of the tumor. In still another instance (case 12) the intrapontile location of the tumor, in the absence of any signs of a primary focus elsewhere, hindered the recognition of the metastatic nature of the neoplasm.

CASE 9.—*Acute onset of cerebral manifestations of seven weeks' duration. Diagnosis of tumor in the left frontal region. Craniotomy; no tumor revealed. Rapid decline; death. Necropsy: neoplasm (later recognized as carcinoma) in the left superior parietal lobule.*

History.—W. E., a clerk aged 46, entered the hospital on March 25, 1917. His fatal illness began three months earlier (Dec. 15, 1916), when he had a sudden attack of vertigo. Somewhat later his speech was noted to be thick; within two weeks after the onset he passed through another episode of dizziness, with loss of consciousness. This was followed ten days later by a third attack, which was characterized by vomiting, dizziness and temporary loss of consciousness. Frequent attacks of headache and mild right hemiparesis with paresthesia developed somewhat later. Vomiting became more frequent and was projectile; speech and ability to read and write became impaired.

Examination.—The patient was dull and apathetic. The neurologic findings included motor aphasia, bilateral weakness of the external rectus muscle, bilateral papilledema of moderate degree, right hemiparesis, hyperreflexia and a Babinski sign on the right side, a mild Kernig sign bilaterally, slight rigidity of the neck and definite tenderness on percussion over the left frontal region. Roentgenograms of the skull showed slight enlargement of the sella turcica, with absorption of the anterior and posterior clinoid processes. Examination of the cerebrospinal fluid, blood and urine gave normal results.

Course.—A diagnosis of cerebral neoplasm in the left frontal region was made. An exploratory craniotomy with right subtemporal decompression, carried out on March 27, the second day in the hospital, failed to reveal any tumor. The patient's condition declined rapidly; signs of terminal pulmonary involvement developed, and he died on the ninth day in the hospital.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: The left cerebral hemisphere was decidedly larger than the right, the enlargement being most noticeable in the region of the parietal lobe. The left hemisphere in this region measured 8 cm. from the sagittal fissure outward to the periphery, at the level of the posterior commissure. The right hemisphere measured 6.5 cm. There was enlargement of the left hemisphere dorsoventrally in the same section. The convolutions of the left hemisphere were much flattened, especially in the region of the superior parietal lobule, and the fissures in the same region were shallow.

The bulging of the parietal lobe was especially well marked in the region of the interparietal fissure, at its intersection with the postcentral fissure. A section of the brain showed that the bodies of the lateral ventricles were only slightly dilated. The corpus callosum was displaced to the right, about 1 cm. beyond the midline. A neoplasm, about 4 cm. in diameter, lay beneath the cortex, almost entirely within the area of the superior parietal lobule. It was surrounded by an area of softening, varying in thickness from 1 to 2 cm., which demarcated the tumor from the surrounding brain substance. Only a thin layer of cortex overlay the tumor, which was undisturbed.

Microscopic Observations: The tumor consisted of small islands of neoplastic cells distributed irregularly in necrotic tissue. The tumor cells were in various states of preservation, ranging from cells which were clearly and distinctly outlined to those which had undergone almost complete disintegration. The better preserved cells were columnar, with the nucleus almost always placed at the base of the cell. The cells were arranged either as acini containing a central space, sometimes filled with a mucinous material, or as papillomatous formations with a number of villus-like projections containing a central core of connective tissue, in which ramified a number of thin-walled blood vessels.

The signs pointing to a well localized lesion in the presence of evidence of increased intracranial pressure led to the diagnosis of a primary cerebral neoplasm. Even the acuteness of the onset and the rapidity with which the symptoms and signs developed need not have been interpreted as evidence of the metastatic character of the neoplasm, though indicating a malignant and rapidly growing tumor. A single lesion, such as that in this case, is not common, but when it occurs it offers some hope for operative intervention, even when its metastatic character is suspected, for the mass may be removable. Moreover, little is lost if the subsequent course is not altered by the surgical treatment.

CASE 10.—*Acute onset of cerebral manifestations of three months' duration. Symptoms of increased intracranial tension, followed by development of signs of meningeal irritation. Diagnosis of tumor in the posterior fossa. Suboccipital exploration. Malignant character of the tumor recognized. Second partial removal of tumor tissue. Fatal termination. Necropsy: multiple metastatic sarcoma.*

History.—B. G., a schoolboy aged 10, had been well except for an attack of diphtheria at the age of 7 and of measles at the age of 9 years. He was brought to the hospital on Aug. 4, 1923, with the history of sudden onset of the illness about three months earlier. He suddenly vomited one morning, and thereafter attacks of vomiting recurred every three to seven days. A month later headache developed, which at first was generalized but later became localized to the right frontal region. General numbness, of which the patient complained at the onset of his illness, had become localized to the left half of the body. The last two months of life were marked by double vision, a buzzing sensation in the left ear and shooting pain in the left leg.

Examination.—The boy appeared to be poorly developed and anemic. He was somewhat drowsy and apathetic and complained constantly of pain in the right temple, where tenderness was elicited on percussion. There were bilateral papilledema, with temporal contraction of both visual fields, bilateral ptosis, weakness of left externus rectus muscle, horizontal nystagmus to the left, deviation of the

tongue to the left, left hemiparesis, with slight tremor of the left hand, increased knee and ankle reflexes on the left side and diminished abdominal reflexes and absence of the cremasteric reflex on the same side. There were also left hemihypesthesia and hemihypalgesia, slight rigidity of the neck and a slight Kernig sign bilaterally. A positive Weber sign was elicited on the right. Examination of the blood, cerebrospinal fluid and urine yielded no significant results.

Course.—Among the diagnostic possibilities, that of a neoplasm in the brain stem blocking the interventricular communications or, more precisely, of an ependymoma in the aqueduct of Sylvius was considered. A neoplasm in the posterior fossa was finally accepted as the more likely diagnosis. Suboccipital craniotomy revealed two grayish masses in the right cerebellar lobe. They seemed to be under the leptomeninges and not to have involved the brain tissue proper. The nodules had a lymphoid appearance and were thought to be metastatic sarcomas.

The operation was followed by initial improvement in the general condition, without a change in the neurologic signs. After a period of convalescence, the patient was allowed to return home. Ten days later (August 2) he complained of severe headache, began to vomit, became aphasic and lost power in all extremities. He gradually passed into stupor, and in this condition he was returned to the hospital. Pronounced herniation of the operative area was noted. Weakness of the right side of the face, spontaneous nystagmus in all directions, dilated and unequal pupils, generalized hypotonia, with loss of all deep reflexes, and bilateral papilledema were observed objectively. A fragment of tumor tissue from the right cerebellar hemisphere was removed on August 17 through the old wound. The patient died two days later.

Necropsy (examination limited to the cranium).—Gross Anatomic Change: The brain was removed through a small surgical opening. The pia-arachnoid showed no macroscopic changes. The gyri were flattened and in a few places showed slight elevations and increased consistency. At such areas, on incision, small nodules, measuring from 0.5 to 1.0 cm., were observed, suggesting small metastatic sarcomas. Nodules were found in the following sites: (1) the anterior portion of the upper frontal convolutions on the left side; (2) in same convolutions, 2 cm. posterior to the first nodule; (3) on the floor of the circular sulcus; (4) in the right occipital lobe and (5) in the cerebellum. The cerebellum was swollen, and the left lobe was extremely soft and fragile; on its upper surface it presented a hemorrhagic, apparently neoplastic, mass.

Microscopic Observations: Sections through the cerebellar tumor showed it to be highly vascular and cellular. Sections through the smaller tumor nodules revealed rounded neoplastic masses, which were distinctly marked off from the rest of the brain tissue and were made up of cells of uniform type, somewhat oblong and rich in nuclear material, which stained deeply. In their arrangement the cells had a tendency to collect about and encircle blood vessels. The brain tissue directly adjacent to the neoplastic mass presented blood vessels, the adventitial spaces of which were infiltrated with cells of a similar type. In many instances such cells apparently had broken through the adventitial coat and had infiltrated the extravascular territory. Similarly, the tumor tissue had invaded the pia-arachnoid space and extended into the contiguous brain substance by perivascular channels communicating with that space.

The signs of increased intracranial tension with rapidly developing bilateral papilledema pointed strongly to the presence of an intracranial tumor. The disseminated character of the lesion, evidenced by apparent

implication of the eighth and third nerves, the meningeal irritation and the involvement of the brain stem, pointed to the main localization of the lesion in the posterior fossa. Other signs suggested multiplicity of the lesions and should have aroused the suspicion of its metastatic character.

CASE 11.—*A mass in the right parietal region of four months' duration, disclosed at craniotomy as a tumor apparently arising in the brain; histologic diagnosis, hemangioendothelioma. Similar observations at three subsequent craniotomies. Final attempt at removal of the tumor was followed by death. Necropsy: metastatic (Grawitz) tumor in the right parietal region.*

History.—A woman aged 50 entered the hospital for the first time on Nov. 1, 1935 because of a growth on the top of her head, which she had had for four months. A previous attempt to remove it, in the belief that it was a sebaceous cyst, had to be abandoned because of profuse bleeding. It was then noted that the lesion had involved the calvarium.

On entering this hospital she also complained of pain in the left hip. No neurologic signs of intracranial tumor were found, but roentgen examination of the head showed erosion of the bone in the right parietal region. Craniotomy was then performed, and a tumor 3 cm. in the long diameter, apparently springing from the intracranial contents in the right parietal region, was observed. An exposed part of this growth was removed.

A report of the microscopic study of the obtained tissue follows: "A section of the tumor presented on one side a dense layer of connective tissue, which had the appearance of dura. Underneath this were fairly solid masses of tumor cells. The great majority of the cells were somewhat elongated and had the appearance of endothelium. They were blocked out into small nodules by a fine stroma of fibroblasts and throughout the tumor surrounded numerous thin-walled vascular channels, filled with blood. Another section taken from the tumor confirmed the provisional diagnosis of meningioma. However, the presence of numerous sinusoids, some filled with blood and surrounded by endothelial-like cells, suggested a modified diagnosis of meningioma of the hemangioendotheliomatous type."

The patient made an uneventful recovery from the operation and left the hospital ten days after admission. Three weeks later the pain in the left thigh reappeared, and she returned to the hospital on Jan. 17, 1936.

Examination.—There was moderate sclerosis of the retinal vessels. The left palpebral fissure was wider than the right. The left knee jerk was somewhat depressed. There was some pain in the lower part of the spine, and tenderness was elicited on deep pressure over the left sacroiliac spine. The patient was emotionally unstable. The blood pressure was 250 systolic and 140 diastolic.

Laboratory Data.—A lumbar puncture yielded clear, colorless cerebrospinal fluid under an initial pressure of 190 mm. of water. There were 5 mononuclear cells per cubic millimeter; the total protein was 54 mg. per hundred cubic centimeters; the Ayala index was 5.7. The colloidal gold curve was normal, and the Wassermann reaction was negative. A blood count was within normal limits. Urinalysis revealed many white blood cells, but nothing else of significance.

Course.—Three days after admission (on January 20) weakness and further reduction in the deep reflexes of the left lower extremity were noted. Roentgen examination of the left hip and femur and the lumbosacral portion of the spine revealed no bony abnormalities. A flat roentgenogram of the skull showed "striations," which were interpreted as suggestive of a meningioma of the right parietal region. Removal of the residual tumor was thought advisable and three attempts were made, each precipitating troublesome bleeding. Some tissue was removed

at the second attempt (on February 1). Again, the diagnosis of hemangioendothelioma was made, but later, on reexamining the section, its similarity to tissue subsequently removed for biopsy was recognized (fig. 8 *A*).

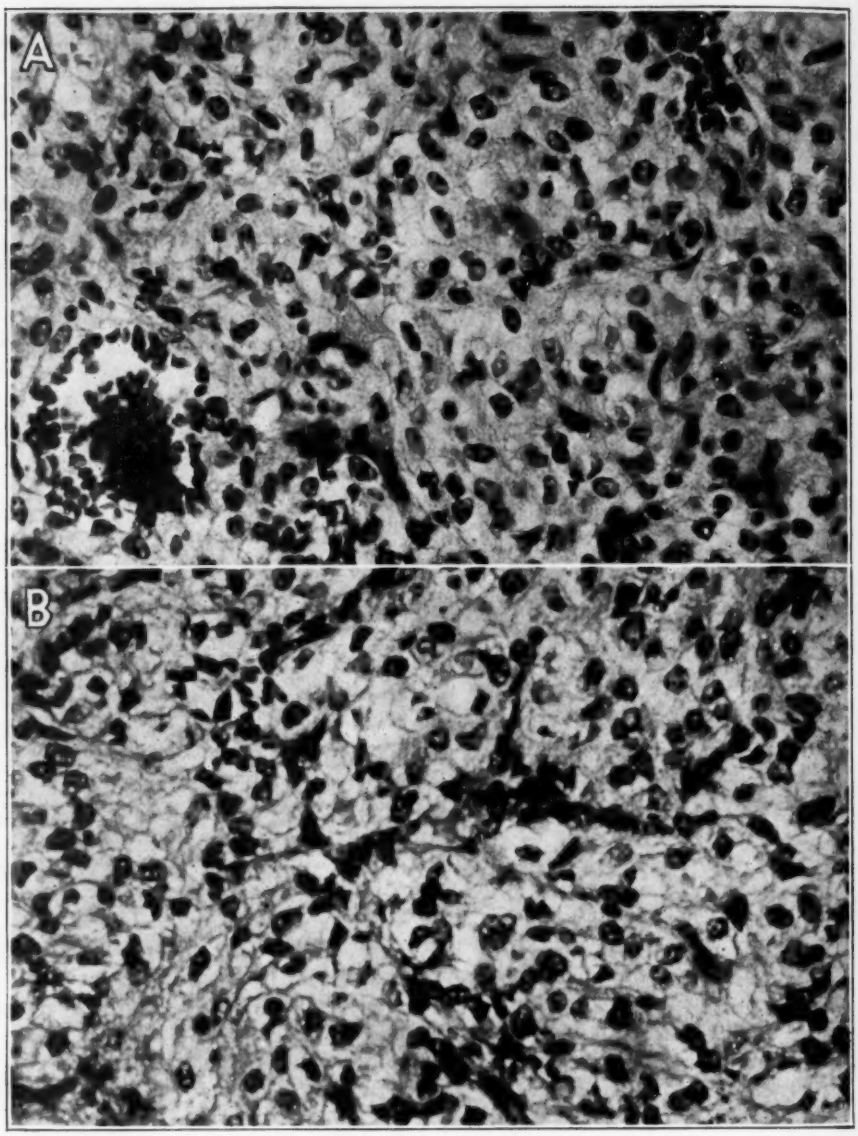

Fig. 8 (case 11).—*A*, section of material removed for biopsy at second operation and originally diagnosed as meningioma. × 425.

B, section of tumor removed at the final operation, diagnosed as a metastatic tumor and later, after autopsy, identified as a Grawitz tumor. × 445.

A third surgical intervention (March 12) yielded tissue which was identified as that of a metastatic tumor (fig. 8 *B*). Death followed twenty-four hours after the operation.

Necropsy.—Gross Anatomic Changes: At the junction of the fissure of Rolando and the longitudinal fissure was an area of cortex about the size of a quarter which was intensely hyperemic and blood stained. There were several silver clips in this zone. The leptomeninges were thickened and adherent to the dura mater. On sectioning the brain, an area of discoloration was observed in the right hemisphere near the dorsal border in the region of the precentral and postcentral gyri. Several vessels were closed by silver clips, and many small petechial hemorrhages were noted.

Microscopic Observations: Sections of the brain in the region of the operative defect disclosed tumor tissue, the architecture of which showed great variability. Some areas were densely cellular; others were sparsely so and contained numerous capillaries. Still other areas consisted of robust collagenous fibers. The nuclei were small, round or oval, and contained a good deal of chromatin material. The tumor was seen to infiltrate the dura, pieces of which adhered to it. Zones of necrotic material or frank hemorrhages were observed. In some places multinucleated foreign body giant cells were present. The leptomeninges were thickened by the increase of connective tissue fibers and accumulations of macrophages containing brownish pigment granules. In the surrounding cortex the ganglion cells showed varied stages of degeneration and some petechial hemorrhages were found. The neoplasm was recognized as a Grawitz tumor.

Of interest in this case is the discovery of the primary malignant focus and the final recognition of the metastatic character of the cerebral lesion. On restudying the early surgical material and comparing it with the final biopsy material, it becomes apparent that the metastatic nature of the lesion should have been recognized earlier (fig. 8 *B*). The failure to do so resulted from the fact that a less characteristic part of the tumor came under microscopic study.

CASE 12.—*Acute onset of signs and symptoms pointing to bulbar involvement. Diagnosis of infiltrating tumor of the pons. Roentgen therapy. Progressive decline; death. Necropsy: metastatic carcinoma in the pons, primary in the lung.*

History.—D. S., a man aged 56, entered the hospital on three occasions during a period of six months (September 1940 to March 1941). His illness began two months before his first admission with impairment of handwriting. One week later he began to experience double vision on looking to the left, and his speech became slurred. The succeeding weeks were marked by progressive increase in weakness of his arms and legs. While the left extremities seemed to improve in strength, the weakness of the right arm and leg remained unchanged. Three weeks before admission to the hospital intermittent headaches, increasing in severity, set in. They were accompanied by a disturbing drilling noise in the left side of the head. Shortly thereafter the patient found that he could not completely close his left eye and that the muscles on the left side of the face were weak; hearing in his left ear became impaired.

Examination (first admission, September 13).—Horizontal nystagmus on left lateral gaze and rotatory nystagmus on upward gaze; palsy of the left external rectus muscle; hypesthesia of the left cornea; weakness of the left side of the face

of peripheral type; diminution of hearing on the same side, with deviation of the tongue to the left; deviation of the soft palate to the right; slurring of speech; weakness and hyperactive deep reflexes, with an equivocal Babinski sign on the left side, and reduced perception of pain on the entire right side, including that of the head, were the more significant neurologic findings. There was bilateral ataxia on finger to nose and heel to knee tests, more noticeable on the right side. The gait was broad based and unsteady.

Laboratory Data.—Roentgen examinations of the skull and of the chest were reported to show nothing significant. Complete examination of the blood and urine gave normal results.

Course.—The presence of a neoplasm in the brain stem was considered, with the possibility of a vascular lesion not entirely excluded. Roentgen therapy was begun, but the first treatment provoked an untoward reaction and hence this form of therapy was discontinued. The neurologic status remained unaltered, and the patient was allowed to leave the hospital on October 16. There was at first temporary improvement in power, but vision and hearing grew worse and the weakness of the right arm and leg increased. He began to experience difficulty in swallowing and reentered the hospital on November 20.

Examination (second admission).—There were nystagmus on right lateral gaze, paralysis of the left external rectus muscle and right hemiparesis, with a Hoffmann sign and ankle clonus on the same side. There was partial paralysis of the left facial nerve of peripheral type. Speech was thick and slurred, and swallowing was difficult.

Course.—Lumbar puncture yielded cerebrospinal fluid under an initial pressure of 300 mm. of water. The Pandy reaction was 4 plus, and there were 11 large mononuclear cells per cubic millimeter. The diagnosis of an infiltrating neoplasm in the brain stem was now accepted. The patient was subjected to roentgen therapy for four weeks, with little if any improvement, and was discharged to return home (December 28). During the following three and a half months his condition declined progressively, and when he reentered the hospital for the third time he was in very poor condition.

Examination (third admission).—There were no new neurologic signs. A lumbar puncture yielded cerebrospinal fluid under an initial pressure of 190 mm. of water. The cell count was 30 per cubic millimeter, and the Pandy reaction was 4 plus. A rapid decline terminated in death.

Necropsy.—Gross Anatomic Changes: The pons was the seat of a large tumor. Its greatest dimension was at the level of the lower portion of the pons, where it occupied practically all the tegmentum and part of the basis pontis, leaving a narrow zone dorsally and a still narrower one ventrally (fig. 9). The structures medial to that mass were displaced to the right and compressed. At that point the lesion was circular and was sharply demarcated from the adjacent edematous tissue. When traced anteriorly, the mass was observed to terminate at the level of the nucleus of the trigeminal nerve, leaving the lateral pyramidal tracts uninvolved.

Microscopic Observations: The tumor mass consisted of columns of neoplastic cells, each zone being separated by a connective tissue stroma, in which ramified numerous blood vessels. There was a tendency for the neoplastic cells to form acini, and in such instances the cells were typically columnar, with a small, moderately chromatinized nucleus situated at the base of the cell. The center of the acini contained some desquamated epithelial cells, with a few lympho-

cytes and polymorphonuclear leukocytes. Usually the neoplastic cells formed broad sheets with no semblance of acini formation. In such instances the cells were necrotic and assumed bizarre shapes and sizes. Intermingled with these were also necrotic blood elements and macrophages. That part of the brain adjacent to the tumor showed evidence of reaction. There were degenerative alterations in the ganglion cells, tissue rarefaction, glial proliferation, ameboid glia cells, perivascular lymphocytosis and vascular congestion.

General Autopsy Observations.—A carcinoma, which appeared to arise from the bronchus, was observed in the upper lobe of the right lung.

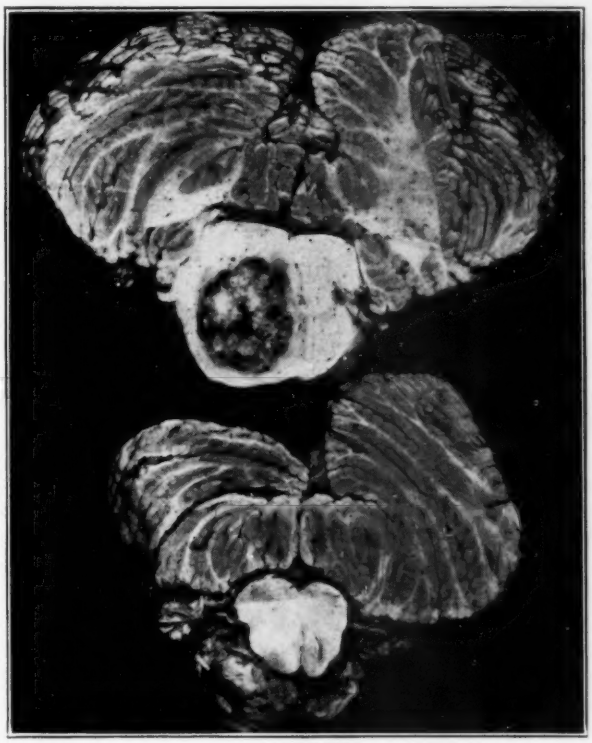

Fig. 9 (case 12).—Sections of the brain stem with the overlying cerebellum, showing the character and location of the tumor (in the tegmentum of the pons). Note its projection ventrad to the medulla in the lower section.

The clinical picture pointed to a circumscribed pontile lesion. The negative roentgenograms of the chest, of course, disarmed the slightest suspicion of metastasis.

GROUP 4: *Metastatic character of the cerebral tumor recognized, but no primary focus discovered* (13 cases).—In spite of all available methods of examination, no definite clinical proof was obtained in any of the cases included in this group to implicate any organ other than the brain as the seat of the primary focus. In 1 instance, because of a low hydro-

chloric acid content, the stomach was suspected, but postmortem examination failed to disclose neoplastic disease of this organ and the primary focus was found in the left lung.

CASE 13.—*Acute onset of cerebral manifestations, followed by development of signs of intracranial tension. Focal signs meager. Diagnosis of brain tumor; its metastatic character suspected. Rapid decline; death. Necropsy: multiple metastatic carcinoma of the brain.*

History.—A. F., a man aged 55, dated the beginning of his illness three months before his admission to the hospital (Feb. 28, 1928), the onset being marked by an unusually long period (thirty-six hours) of sound, uninterrupted sleep. It was followed by pain in the right arm and hand. Infected teeth were extracted in the belief that they were the cause of his pain. Two weeks after the onset of the pain severe headaches set in, followed shortly by progressive impairment of vision. About the same time memory began to fail.

Examination.—The patient was confused and disoriented. There was slight blurring of the disks. The pupils were unequal and irregular, the right pupil reacting sluggishly to light and in accommodation. There was weakness of the left side of the face of central type. All the extremities were spastic, those on the left side being weaker than those on the right. The left upper extremity was held in a position of semiflexion at the elbow. The deep reflexes on the left side were hyperactive; the abdominal reflexes were depressed. There was moderate rigidity of the neck, and a Kernig sign was elicited.

Laboratory Data.—The cerebrospinal fluid was under slightly increased pressure. It was clear, free of cells and otherwise normal. All other laboratory studies gave normal results.

Course.—A diagnosis of cerebral neoplasm was made, but the location of the tumor was in doubt. As hoarseness developed and the patient experienced difficulty in swallowing, it was thought advisable to look elsewhere for the lesion. Accordingly, a roentgenographic examination of the chest was performed; this revealed an oval shadow 4 inches (10 cm.) in diameter, occupying the middle third of the right side of the chest, which was thought to be a neoplasm. The patient's condition declined rapidly, and he died on the eighth day in the hospital.

Necropsy.—Gross Anatomic Changes: On the inferior surface of the right temporal lobe was a circular area about 3.5 cm. in diameter which was distinctly harder to palpation than the surrounding cerebral tissue. Along the dorsal longitudinal sulcus were two small hard masses, measuring about 1 cm. in diameter; one was situated in the right superior frontal gyrus and the other in the left superior parietal gyrus. Coronal sections of the brain revealed a large tumor in the right temporal lobe; it was 4 cm. in diameter and reached the inferior surface of the right temporal lobe. On the lateral side of the mass was a thin layer of cortical and subcortical tissue; medially the tumor encroached on and compressed the right thalamus. The ventricular system was distorted, the body of the right lateral ventricle being compressed and the left slightly dilated. A second tumor, measuring 1 by 1.5 cm., was located in the superior frontal gyrus of the right cerebral hemisphere; it reached the pia-arachnoid in the dorsomedian fissure. A third tumor, measuring 1 cm. in diameter, was observed in the superior parietal gyrus of the left cerebral hemisphere; it reached the surface of the dorsomedian border of the hemisphere.

The tumors were well delimited from the adjacent cerebral tissue. They were similar in gross appearance; the surface was rough, pale gray and interrupted by dark hemorrhagic areas and numerous small cystlike spaces.

Microscopic Observations: The tumor tissue was for the most part necrotic, especially those portions at the greatest distance from blood vessels. At the periphery of the tumor and interspersed within the necrotic substance were zones of frankly neoplastic tissue. There, strands of connective tissue were seen to divide the tumor cells into smaller groups. Blood vessels ramified within the connective tissue, and occasionally perivascular lymphocytic accumulations were seen.

The neoplastic cells displayed a variety of shapes and sizes; they were predominantly round or oval; some were very large. Similarly, the nuclei varied greatly in size; all were lightly reticulated. There was a tendency in places toward the formation of acini, and in these areas the cells tended to be columnar or cuboidal, with the nucleus at the base of the cell. In one area the tumor cells had invaded the leptomeninges. On the whole, there was a distinct line of demarcation between the tumor and the adjacent brain tissue. In some places, however, small groups of neoplastic cells strayed away from the main tumor mass into surrounding tissue. The latter showed variable degrees of rarefaction, small perivascular hemorrhages and perivascular lymphocytosis.

General Necropsy Observations.—A carcinoma, primary in the lower lobe of the right lung, was observed.

The development of signs pointing to involvement of parts of the nervous system other than the cerebral hemispheres drew attention to the probability of dissemination of the neoplastic process, and hence to its probable metastatic character. This interpretation, in turn, was supported by the roentgenologic signs in the chest suggesting the presence of a mass, which was thought to be neoplastic. The subsequent course and the postmortem observations fully verified this diagnosis.

CASE 14.—*Acute onset of cerebral symptoms of three months' duration; severe headache, followed by vomiting, dimness of vision and drowsiness. Disseminated neurologic signs, accompanied by psychotic manifestations. Rapid decline. Death, without surgical intervention. Necropsy: multiple widespread carcinomatous metastasis (cerebrum and cerebellum).*

History.—S. A., a married man aged 44, was said to have had grip five months prior to his admission to the hospital (Aug. 11, 1923). Two months later he began to complain of severe headache and of pain in the left leg. In another month the headaches were accompanied by frequent attacks of vomiting. At the same time there developed dimness of vision, occasional myoclonic twitching of the abdomen and a tendency to drowsiness. A jacksonian seizure involving the left side, accompanied by loss of consciousness, was followed by the appearance of stiffness in the left hand. Two weeks later there set in an abrupt decline in the condition: He grew weak; speech became thin, and he manifested mental changes. Shortly before admission to the hospital he passed into semistupor.

Examination.—The patient was poorly nourished and in stupor, from which he could be aroused only with difficulty. He appeared to be irrational in the short semilucid periods. There was tenderness to percussion over the left parietal region of the skull. Bilateral papilledema, with retinal hemorrhages and exudates; complete flaccid paralysis of both lower extremities; spastic paralysis of the upper extremities, with weakness more pronounced on the left side; impairment of left conjugate movement of the eyes; deviation of the tongue to the left; hyperactive deep reflexes on the left; absence of the knee and achilles reflexes, and absence of the abdominal reflexes on the left side were among the significant neurologic

findings. Sensory and other fine tests could not be carried out for lack of cooperation. There were no palpable masses or areas of tenderness in the abdomen or thorax. Some bleeding was noted from the rectum, but careful inspection did not disclose its cause and it was thought to be due to injury resulting from the insertion of a rectal tube. A lumbar puncture yielded clear cerebrospinal fluid under greatly increased pressure, containing 12 lymphocytes per cubic millimeter. The Wassermann reactions of the blood and cerebrospinal fluid were negative. The urine contained a trace of albumin and a few white blood cells. A white blood cell count showed 18,400 cells, with 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. Roentgenographic studies showed mild spondylitis. The blood pressure was 140 systolic and 90 diastolic.

Course.—The patient declined steadily and rapidly. Periods of restlessness with hallucinatory episodes were succeeded by a state of stupor. Pronounced emaciation and flaccid paraplegia developed, followed by death on the eighteenth day in the hospital. The disseminated character of the signs suggested multiplicity of lesions, and in view of the afebrile course and negative serologic reactions, the diagnosis of metastatic carcinoma was considered.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: Several nodules, of variable size and firm consistency, were felt in the left cerebral hemisphere. On incision several masses were seen, well demarcated from the adjacent brain tissue. They were granular in appearance and cystic in some parts. One of the nodules, measuring 1 by 2 cm., lay in the frontal pole of the left cerebral hemisphere; another, measuring 2 by 3 cm., was in the posterior portion of the left frontal lobe near the dorsomedian fissure; a third was in the parietal lobe, and a fourth, about 3 cm. in length, extended almost the entire length of the occipital lobe. In the right hemisphere only one small nodule was seen, in the island of Reil. In the cerebellum almost the entire vermis and the adjacent parts of the hemispheres were replaced by a tumor mass, about 4 by 5 cm. in diameter.

Microscopic Observations: Sections of the tumor nodules in the cerebrum and cerebellum showed that the cells were uniform in character and arrangement. They were of squamous type, being flattened against one another, and presented vesicular nuclei, rich in chromatin material and with numerous mitotic figures. In some places the cells assumed a reticular or syncytial character. Large areas of necrotic material or hemorrhages were present, and occasionally a giant cell. The tumor was well demarcated from the adjacent brain tissue.

The marked disorganization of the cerebellum, the compression of the fourth ventricle by tumor tissue and the presence of numerous other metastatic foci in the cerebrum did not permit a satisfactory correlation of the anatomic alterations with the clinical manifestations in this case. It is clear, however, that the varied character of the objective neurologic signs pointed to dissemination of the lesions and that the early appearance of evidence of increased intracranial tension was caused by the large tumor in the region of the fourth ventricle. The psychosis in this instance was a terminal event and need not be regarded as pathognomonic of this type of tumor. The flaccid paralysis and the loss of deep reflexes in the lower extremities suggested the existence of metastatic involvement of the spinal cord and offered further support to the conception that,

with an inflammatory lesion ruled out by the afebrile clinical course and negative serologic reactions, a disseminated pathologic process can with a fair degree of safety be regarded as neoplastic and metastatic.

CASE 15.—*Acute onset of severe headache of six weeks' duration, followed by bilateral tinnitus and unsteadiness in gait. Hard subcutaneous nodules noted in lower right wall of chest. Papilledema; signs of involvement of the pyramidal tract and cerebellum on the left side. Biopsy of subcutaneous nodule revealed metastatic carcinoma; primary focus not discovered. Death five weeks after admission. Necropsy: multiple metastatic carcinoma.*

History.—A man aged 47 had been in fairly good health until six weeks before admission to the hospital, on July 14, 1940, when he suddenly experienced severe pain in the right occipital and cervical regions, lasting for several hours. Subsequently the pain recurred every morning, increased in severity and often lasted throughout the day and the evening. Within one week after the onset of pain he began to complain of noise in both ears, which he described as like "rushing winds." This was followed within two weeks by moderate stiffness of the neck. He became dizzy and unsteady on his feet, until he could not walk without support. On the day of admission he experienced double vision; his left arm became weak, and for the first time the headache was accompanied by nausea and vomiting. Several weeks earlier he had noticed a hard nodule in the lower right anterior wall of the chest.

Examination.—The pupils reacted to light and in accommodation. Convergence was poor, and upward and lateral movements of the eyes were restricted. Papilledema and retinal hemorrhages were present bilaterally. Hearing was somewhat diminished on the left side. The tongue and uvula deviated to the right; the Hoffmann sign was elicited bilaterally and a questionable Babinski sign was obtained on the left side. The abdominal and cremasteric reflexes were absent on the left side. There was a positive Romberg sign, with a tendency to fall to the left. The blood pressure was 165 systolic and 90 diastolic. Subcutaneous nodules were present along the right anterior axillary line. The patient had a moderate cough, and the sputum contained brown and red streaks.

Laboratory Data.—A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 320 mm. of water. There were 31 cells per cubic millimeter. The Pandy reaction was 4 plus, and there was 148 mg. of total protein per hundred cubic centimeters. The Ayala index was 3.7. The Wassermann reaction was negative. The colloidal gold reading was reported as 2222211100. Roentgen examination of the chest revealed nothing significant. A guaiac test of the stool gave a negative reaction. There was 0.006 mg. of lead per hundred cubic centimeters of urine.

Course.—On the day of admission one of the subcutaneous nodules in the lower right side of the chest wall was excised and reported to be a metastatic carcinoma. The cerebral lesion was therefore concluded to be metastatic. It was believed that the tumor was supratentorial, located in the subcortex of the right cerebral hemisphere. The limitation of the eye movements was thought to be due to alterations in the brain stem, secondary to increased intracranial pressure. Another roentgenogram of the chest was reported as negative. The piece of tissue excised at bronchoscopic examination did not show any tumor cells. Electroencephalographic records indicated a deep-seated, expanding lesion in the right cerebral hemisphere. Ventriculographic study was attempted (August 1), but the ventricular system

was not outlined. Repeated lumbar punctures showed continued increase in the intracranial pressure. The patient's condition declined gradually; pneumonia developed, and he died on the fifth week of his stay in the hospital.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: Two tumor masses were observed in the brain. One was situated in the second right frontal convolution and measured 2 by 3 by 3 cm. The tumor was well demarcated from the surrounding tissue and caused downward displacement of the body of the ipsilateral lateral ventricle and flattening of the body of the ventricle on the opposite side. The adjacent tissue showed considerable edema. The second tumor, measuring 2 by 2.5 by 3 cm., was located at the left pontofacial angle and was strongly adherent to the middle cerebellar peduncle and the cerebellar cortex. It deformed the fourth ventricle and displaced it to the opposite side. The cut surfaces of both tumor masses were granular and showed alternating grayish and pinkish colorations.

Microscopic Observations: The tumor tissue consisted of a mosaic arrangement of two types of cells. The dominant type was squamous and large and contained a large, vesicular nucleus. There was considerable variation in the size and shape of both the cell and the nucleus. Occasionally there were several nuclei, some partially fused, in one cell. In rare instances the nucleus was evident as a very small, shrunken, heavily chromatinized mass of material in the center of the cell. The other type of cell was small, with a well formed, moderately chromatinized nucleus, and often looked like a plasma cell. There was a tendency for cells of this type to group themselves about vessels. Areas of necrosis were irregularly scattered throughout the tumor. There were many thin-walled, congested blood vessels. Often one saw such a vessel surrounded by a thin layer of cells of the small type just described, which in turn was surrounded by a thick layer of the large squamous epithelial cells. The tumor was well demarcated from the adjacent brain substance, which showed moderate degenerative alterations in the Purkinje cells.

Here, the subcutaneous nodules revealed the true character of the intracranial lesion and thus established a diagnosis, which otherwise would have offered some difficulty. While the metastatic nature of the neoplastic lesion was recognized, its primary origin remained undisclosed, since complete postmortem observations were not available.

GROUP 5: *Metastatic character of the cerebral tumor recognized and the primary focus clinically identified* (17 cases).—In some cases roentgenologic examination of the lungs revealed the presence of a mass, which was interpreted as neoplastic. In 2 instances roentgenograms failed to reveal evidence of a tumor in the lung, but postmortem examination disclosed the neoplasm. In instances in which the primary lesion was in the thyroid, kidney or gastrointestinal tract, the physical signs pointing to neoplastic involvement were in full evidence.

CASE 16.—*History of recurrent headache. Sudden onset of manifestations of cerebral dysfunction, followed by intensification of headaches and mental changes. Brain tumor diagnosed, its metastatic character recognized and the primary lesion (carcinoma of the sigmoid portion of the colon) identified.*

History.—A man aged 58 had been subject to periodic frontal and occipital headaches for many years. They occurred weekly, lasted a few hours and were

relieved by acetylsalicylic acid or black coffee. Occasionally they were associated with periods of dizziness. At the age of 52, while at work, he suddenly "collapsed" and remained in a daze for several minutes. Four months before his admission to the hospital his headaches had become more frequent, more severe and generalized and were accompanied by dizziness. Shortly thereafter he began to complain of intermittent sharp pain in his chest and the upper part of his back, which was aggravated by deep inspirations. At a clinic he was found to have advanced scoliosis, an "aortic type of heart," old fibrosis at the roots of the bronchi, with central productive thickening, probable old scarring in the upper lobes of the lungs and probable slight pleural thickening over the apexes, chiefly the left. Four weeks before entering the hospital he collapsed again. At this time he was nauseated, vomited repeatedly and suffered from severe headache, which no longer yielded to medication. In the course of the following weeks he lost weight and was said to have had very dark stools on several occasions. Walking became difficult, and two weeks after his "collapse" he took to bed. He entered the hospital on Sept. 26, 1936.

Examination.—The patient walked unsteadily and tended to fall to the right. There were stiffness of the neck and a positive Brudzinski sign. The pupils were unequal, the left being larger than the right; both reacted well to light and in accommodation. The fundi showed moderate arteriosclerosis. The left palpebral fissure was larger than the right. There was weakness of the left side of the face of central type. The left arm tended to drift slightly from position when extended. The left arm displayed slight clumsiness on carrying out rapid alternating movements. There was slight terminal unsteadiness on the left side during the finger to nose test. The deep reflexes were increased in the left upper extremity, while the right ankle jerk was more active than the left. Babinski and Chaddock signs were present on the left side. Lasègue and Patrick signs were noted bilaterally. The patient was pale, apathetic and emaciated. His skin was yellow. The dorsal vertebrae were tender on percussion. The cervical and inguinal lymph glands were enlarged. The appexes of both lungs were dull on percussion. The liver was slightly enlarged, and the prostate was somewhat nodular. The blood pressure was 140 systolic and 105 diastolic.

Laboratory Data.—Lumbar puncture yielded clear, colorless cerebrospinal fluid, containing 3 cells per cubic millimeter. The total protein was 69 mg. per hundred cubic centimeters; the Queckenstedt reaction was negative, and the Pandy reaction was 1 plus. Roentgen examination of the chest showed old healed tuberculous lesions at both apexes. The roentgenogram of the spine displayed rarefaction and collapse of the fourth dorsal vertebra, while that of the skull was reported to be normal. Caloric tests gave normal vestibular responses. The Wassermann reactions of the blood and cerebrospinal fluid were negative, and the results of urinalysis were normal.

Course.—The diagnosis of a neoplasm in the right cerebral hemisphere was considered as the more likely, but cerebral arteriosclerosis with a focal lesion in the right cerebral hemisphere could not be fully excluded. Headaches continued during the two days following admission; they were severe, did not abate with medication and were occasionally accompanied by vomiting. On the fourth day in the hospital papilledema appeared in the left eye. With the roentgenologic report indicating rarefaction and collapse of the fourth dorsal vertebra, the diagnosis of multiple metastases, with the primary focus probably in the gastrointestinal tract, was made. (The prostate was reexamined and was excluded as the seat of the primary focus.) Examination of the gastrointestinal tract was reported as showing

an incomplete intestinal obstruction. The patient became progressively weaker; the papilledema continued to advance, and hemorrhages appeared in the disks. Two weeks after admission a firm, irregular mass was observed in the abdomen just above the umbilicus. Ten days later another mass appeared in the right flank.

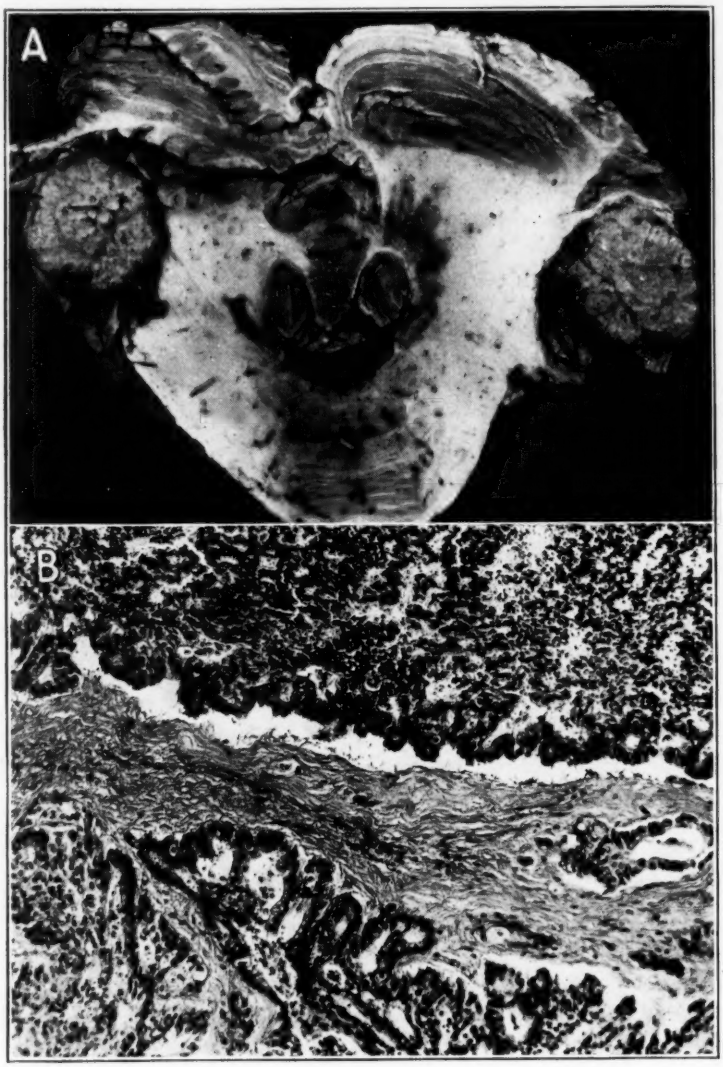

Fig. 10 (case 16).—*A*, coronal section of the brain stem, showing bilateral and symmetrically located metastatic tumors.

B, histologic character of the tumor. × 55.

The patient's condition continued to decline steadily, and he died on November 3, five weeks after admission.

Necropsy.—Gross Anatomic Changes: On the ventral aspect of each cerebellar lobe was a large, hard, but friable mass. Each mass was spherical, and its lateral

surface was adherent to the dura mater. The mass on the left measured 3 cm. in diameter; the one on the right was somewhat larger. A small nodule was found adherent to the dura mater on the under surface of the tentorium. On sectioning the brain, the ventricular system was observed to be greatly dilated. The two tumor masses aforementioned were lodged in shallow depressions under the middle cerebellar peduncles (fig. 10 *A*).

Microscopic Observations: Sections of the tumor stained with hematoxylin and eosin showed masses of cells, which assumed a glandular arrangement (fig. 10 *B*). Two types of cells were present. One type, which lined the acini, was fairly large and contained a similarly large, but pale, nucleus at the base of the cell. The second type, which was widely distributed throughout the supporting connective tissue, was a small cell with a darkly staining nucleus. Throughout the tissue there were masses of cells in various stages of necrosis. In some areas disintegration had advanced to the point where no cellular details could be discerned.

General Necropsy Observations.—An annular carcinoma of the sigmoid portion of the colon, causing partial obstruction, was observed. Metastatic lesions were present in the lungs and the thoracic vertebrae.

It is probable that the dissemination of the metastatic process to the brain dated back to the time that intense headaches made their first appearance (four months before admission to the hospital). It corresponded to the time the patient began to complain of pain in the chest and spine, marking the arrival of the metastatic tissue in the lungs and, probably, the vertebrae. The symmetric development of the metastases in the region of the middle cerebellar peduncles indicates the synchronous distribution of the metastatic seedlings.

CASE 17.—*Cerebral symptoms of four weeks' duration. History of previous removal of malignant tumor of the face. Development of acute signs and symptoms of increased intracranial tension. Disseminated objective neurologic signs. Rapid decline. Death, without operative intervention. Necropsy: metastatic melanocarcinoma in the right occipital lobe.*

History.—L. J., an engraver aged 29, entered the hospital June 14, 1924, complaining of headache and dizziness. Two years previously a tumor was removed from his cheek which at that time was considered to be a squamous cell carcinoma. He was apparently doing well for about twenty months, when he began to experience headache and recurrent attacks of dizziness. Impairment of vision followed, and somewhat later diplopia and attacks of vomiting developed.

Examination.—The positive neurologic findings included unequal pupils, the right being larger than the left, both reacting normally to light and in accommodation; bilateral rotary nystagmus; bilateral exophthalmos; bilateral corneal hyperesthesia; bilateral papilledema; a defect in the left homonymous field; bilateral weakness of the external rectus muscle; bilateral facial paresis, more pronounced on the right, and weakness of the muscles of mastication on the right side. Chemical studies of the blood, Wassermann tests of the blood and cerebrospinal fluid and urinalysis all gave normal results. Twice repeated roentgenographic examinations of the skull were reported to show nothing abnormal.

Course.—The diagnosis of a cerebral neoplasm, most likely suprasellar, was considered. In view of the history of previous removal of a malignant tumor, the metastatic character of the lesion was strongly suspected. The stay in the hospital

was marked by progressive decline in the general condition and by advancing papilledema. In an attempt to save the sight, bilateral subtemporal decompressions were performed, but this did not interrupt the steady decline. The patient died about five weeks after his admission to the hospital.

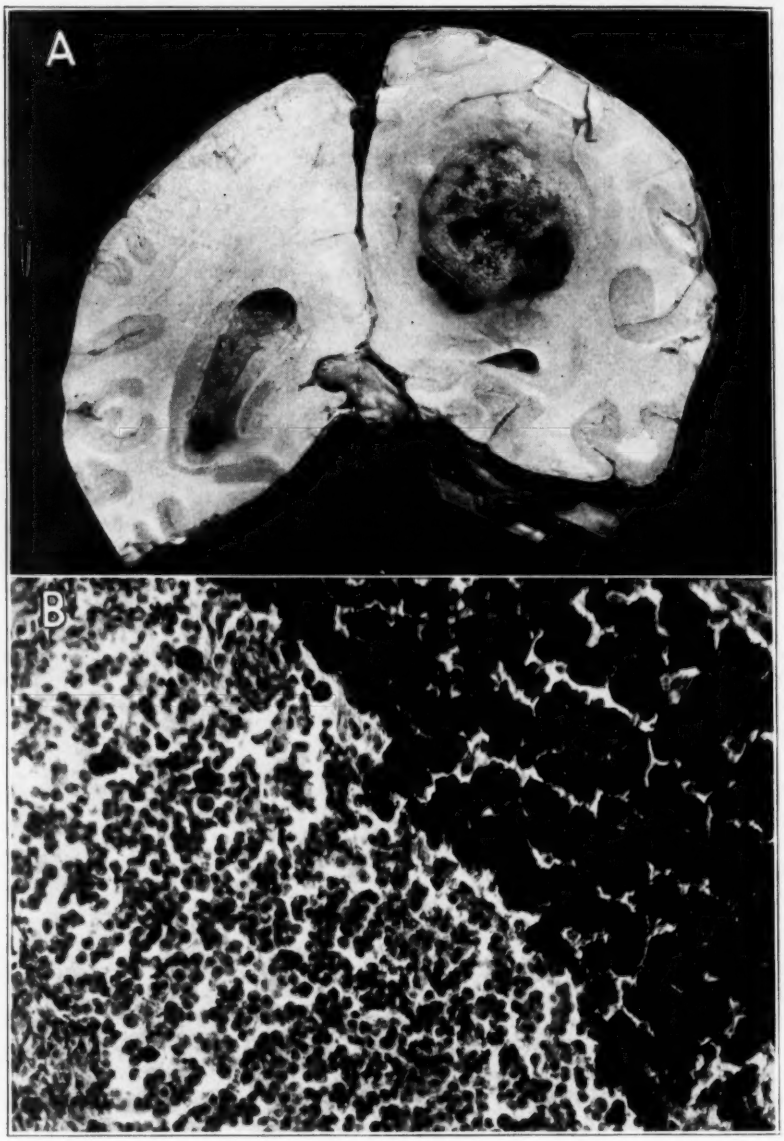

Fig. 11 (case 17).—*A*, coronal section of the cerebral hemispheres, showing the gross appearance and location of the metastatic melanoblastoma.

B, histologic appearance of the tumor, showing large collections of melanin-laden cells. × 200.

Necropsy (examination limited to the cranium).—Gross Anatomic Changes: In the right occipital region a discolored area was noted, in the center of which was a small opening through which clear yellowish fluid was slowly exuding. When an incision was made at this level, a large neoplastic mass was observed, nodular in structure, granular in appearance and varying from pearly white in some areas to brownish red in others (fig. 11 *A*).

Microscopic Observations: A section through the most typical portion of the neoplasm presented a fairly uniform picture (fig. 11 *B*), not unlike that in case 1. Here, cells of three varieties were seen: (1) polygonal cells, containing large, round, vesicular nuclei, which were grouped about blood vessels, giving the impression of an arrangement seen in perithelioma; (2) fusiform cells, forming bands encircling the cell nests previously described, and (3) round cells, with small, pyknotic nuclei, filled with a coarse, brown pigment. Numerous mitotic figures were seen everywhere, and large areas of extravasation were encountered.

The acute onset of headache and dizziness, with the development of objective neurologic signs pointing to a disseminated lesion, such as the fixed facies and the diplopia, resulting from bilateral weakness of the external rectus muscle, could be considered as pointing to an encephalitic process were it not for the hemianopia and bilateral papilledema, signs that warned of an expanding lesion. The history of a neoplasm elsewhere made the metastatic character of the lesion probable.

The anatomic observations can be readily correlated with the clinical manifestations. This is particularly true of the left homonymous hemianopia, with the tumor mass almost completely replacing the right occipital lobe. The bilaterality of some of the signs suggested at one time a suprasellar localization. A neoplasm of such size and location, by compressing the third ventricle, resulting in obstructive hydrocephalus, is a likely cause of such a manifestation.

CASE 18.—*Pulmonary signs and enlargement of the thyroid gland of two months' duration. No neurologic signs until the day before death, paresis of the right arm preceding the fatal end by one day. Necropsy: carcinoma of the thyroid gland, with generalized metastases to various organs, including left frontal lobe.*

History.—A woman aged 60 was first observed in the medical service of the hospital on March 17, 1925. She had a cough productive of blood-tinged sputum two months before her admission. While the cough subsided, there developed severe pain in the right side of the chest. The pain gradually diminished, and she remained symptom free until the day of admission, when the pain in the chest and the blood-tinged sputum returned.

Examination.—The chest was emphysematous; moist rales were heard at the bases of both lungs. The liver was enlarged, its lower border being felt 3 finger-breadths below the costal margin. The lateral lobes of the thyroid were enlarged and firm. There were no neurologic signs.

Laboratory Data.—Roentgenographic examination of the chest showed healed processes at the apexes of the lungs. The left ventricle was dilated and hypertrophied. Examinations of the blood and urine revealed nothing abnormal. The blood pressure was 120 systolic and 60 diastolic.

Course.—The diagnosis at first was that of generalized arteriosclerosis, pulmonary infarction, myocardial insufficiency and probable malignant neoplasm of the thyroid, which had become calcified. A mass in the right upper quadrant of the abdomen was soon noted, and shortly thereafter several hard masses appeared in the left infraclavicular region and over the left scapula. Paresis of the right arm followed, and the diagnosis of a malignant growth in the thyroid with generalized metastasis to various organs, including the brain, was made. The paresis marked the onset of a rapid decline, which led to a fatal end on the following day, two and a half weeks after admission.

Necropsy.—Gross Anatomic Changes: On sectioning the brain, several small metastatic nodules were seen in the left cerebral hemisphere. One was situated in the left frontal lobe close to the gyrus rectus; another, measuring 1 by 2.5 cm., was observed in the left second frontal convolution near its posterior end, while a third was noted in the left superior frontal convolution at about its middle. All the tumors were well demarcated from the surrounding substance and were granular in appearance and grayish.

Microscopic Observations: The tumor mass consisted of neoplastic cells, areas of necrosis and hemorrhagic extravasations. The neoplastic cells were squamous (epithelial) in type and did not exhibit any particular arrangement, except in places where the connective tissue outgrowths from the blood vessels tended to divide the tumor mass into zones. The tumor cells were large and somewhat oval, although there was great variation in their shape. The nuclei were similarly large and oval, sometimes round and moderately chromatinized, and many showed a well formed nucleolus. Many cells were particularly large and contained several lobulated and partially fused nuclei, giving the impression of foreign body giant cells. Throughout the tumor cells undergoing various stages of mitosis were seen. The vascular supply of the tumor was moderate. The blood vessels were thin walled and congested.

General Autopsy Observations.—A primary carcinoma of the thyroid was observed with metastases to the lungs, heart, liver, right adrenal gland, jejunum and brain.

The age of the patient and the general systemic indications suggested the diagnosis of a cerebral lesion resulting from some vascular disturbance. But the discovery of several disseminated masses led to a rapid diagnostic reorientation in the direction of generalized metastases, including those in the brain, with the primary focus obviously in the thyroid.

CASE 19.—*Several operations for recurring carcinoma of the thyroid. Roentgenographic evidence of metastatic nodules in the chest. Weakness of the right arm, together with convulsive movements, on admission to the hospital. Diagnosis of metastasis to the left precentral gyrus. Progressive decline, terminating in death three weeks after admission. Necropsy: small metastatic nodule in the left precentral gyrus.*

History.—A woman aged 63 had suffered from a recurring carcinoma of the thyroid gland for nine years prior to her admission to the hospital, on Sept. 7, 1939, during which time she was subjected to several operations. One and a half years before admission a roentgenogram of the chest revealed metastatic nodules in the lungs. Three months before admission weakness of the right arm developed, followed by several convulsive attacks affecting that arm. She also complained of left-sided headaches.

Examination.—The pupils were irregular but reacted well to light and in accommodation. There were weakness of the right upper and slight weakness of the right lower extremity. The deep reflexes of the right arm were hyperactive, and the Babinski sign was elicited on the same side.

Laboratory Data.—A roentgenographic examination of the lungs showed shadows which were interpreted as metastatic tumors, while a flat roentgenogram of the skull was reported as showing nothing significant except for some irregular calcific areas along the course of the internal carotid artery.

Course.—A metastatic tumor in the left cerebral hemisphere was considered as the most likely diagnosis, although, because of the patient's age and generalized arteriosclerosis, the possibility of a vascular lesion was also borne in mind. The patient's condition declined rapidly, terminating in death on September 26.

Necropsy.—Gross Anatomic Changes: A flat area was observed in the left hemisphere, in the region of the upper portion of the middle frontal gyrus and in the middle and upper portions of the precentral gyrus. A firm nodule was palpated about 4 cm. to the left of the longitudinal fissure, in the body of the precentral gyrus. This was surrounded by an area of softening, which extended under and beyond the flattened gyri aforementioned. The nodule extended to the surface of the brain through the cortex, where it appeared as a dark area. The vessels at the base were sclerosed. On sectioning the brain, a small tumor, measuring 1.5 cm. in diameter and irregularly circular, was seen in the left precentral gyrus (fig. 12 *A*). The cut surface of the tumor was granular and reddish gray.

Microscopic Observations: The nodule of tumor tissue was well demarcated from the surrounding brain substance. It consisted of neoplastic cells arranged in a papillary, adenomatous fashion, with formation of many acini and cystlike spaces, some of which were filled with a colloid-like material (fig. 12 *B*). The cells lining the spaces were usually cuboidal, but sometimes columnar. The nuclei were small, round and situated at the base. The connective tissue stroma was scant and contained many thin-walled, congested blood vessels. Where the stroma was more abundant, vessels surrounded by rings of lymphocytes were seen. Apart from slight degenerative alterations in the ganglion cells, the surrounding brain tissue did not show any evidences of reaction.

General Necropsy Observations.—Numerous metastatic carcinomatous nodules were observed in both lungs. No tumor tissue remained in the region of the thyroid gland.

It is not without significance that in this group there should be 2 instances of metastatic tumor of the brain in which the primary focus was in the thyroid gland, for the clinical course can be readily traced to so patent a lesion.

GROUP 6: *Malignant disease known to exist, with symptoms pointing to cerebral metastasis absent or appearing as a terminal event.*—The cases in this group offered, of course, no diagnostic problem from a neurologic point of view. In some of the cases neurologic complaints or signs were absent, and the cerebral metastases were discovered only post mortem. Such metastases were small and were located in the so-called silent regions of the brain. When the mental changes appeared as a terminal event they indicated the presence of cerebral metastases.

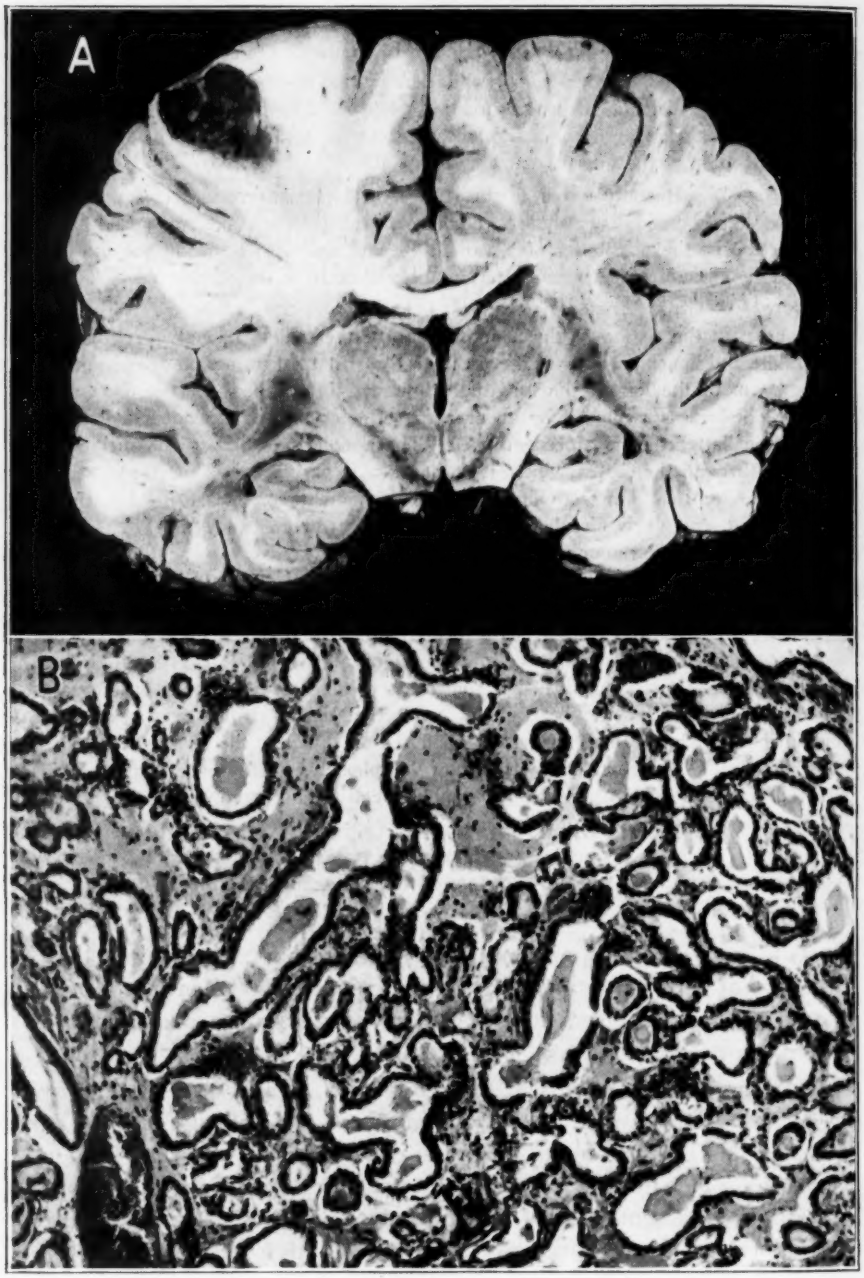

Fig. 12 (case 19).—*A*, coronal section of the brain, showing gross appearance and location of the metastatic tumor.

B, histologic appearance of the metastatic tumor, primary in the thyroid. × 105.

CASE 20.—*Cerebral manifestations occurring during the terminal stage of pulmonary (neoplastic) disease. Rapid decline; death. Necropsy: metastatic carcinoma in perivascular spaces.*

History.—M. C., a man aged 56, was admitted to the medical service of the hospital on June 1, 1923, complaining of rapid loss of weight, a disturbing cough for the preceding five months and shortness of breath for twelve days. The illness began five months earlier with an increase in the severity of the cough, which had been present for about a year. He was in bed for about five weeks and was then allowed to be up for three months. He continued to cough and lost weight rapidly, and more recently the left arm and the left side of the neck had become swollen. The dyspnea became distressing.

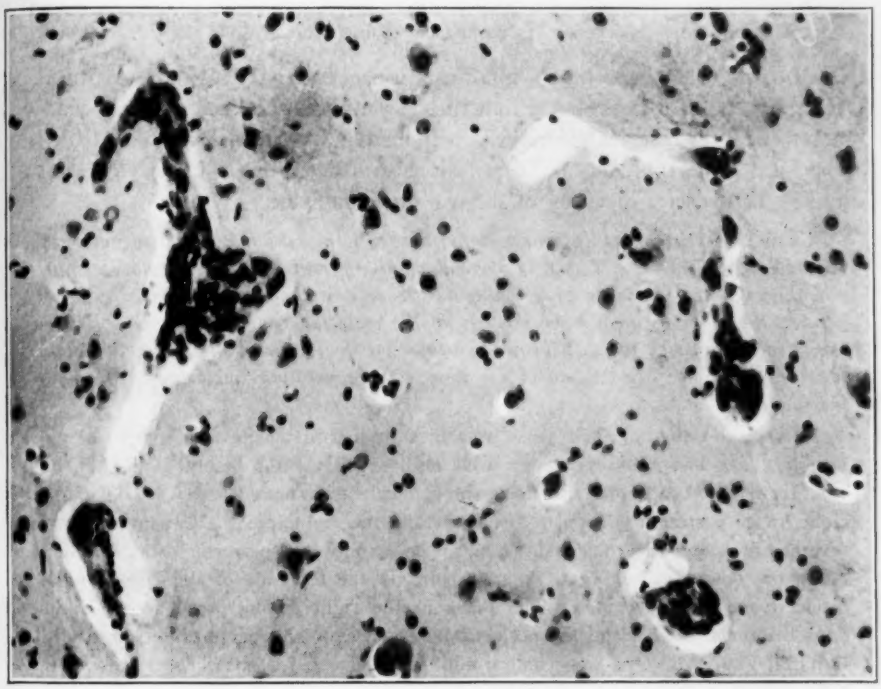

Fig. 13 (case 20).—Section of cerebral cortex, showing perivascular infiltration with tumor cells. × 240.

Examination.—A mass the size of a small hen's egg was felt in the neck on the left side, behind the inner aspect of the left clavicle. Over the upper lobe of the left lung and high up in the axilla anteriorly, there was pronounced dulness, with diminished breath sounds and an occasional moist rale. Two small nodules (neoplastic?) were also felt high up in the rectus abdominis muscles. The patient was severely cyanosed and showed pronounced clubbing of the fingers. Neurologic examination revealed only irregular, but active, pupils. Examination of the urine, cerebrospinal fluid and blood revealed normal characteristics.

Course.—The diagnosis of a neoplasm of the lung with metastasis was made. Several hours after admission the patient suddenly became unconscious, and there

developed Cheyne-Stokes breathing, bilateral corneal anesthesia, conjugate deviation of the eyes to the left and left hemiplegia, with signs of involvement of the pyramidal tract on that side. The condition rapidly declined. On the following day complete quadriplegia, with a bilateral Babinski sign and loss of abdominal reflexes, developed. The patient died without regaining consciousness on the third day in the hospital.

Necropsy.—No gross pathologic lesions were found in the brain substance, but microscopic examination revealed isolated areas in which carcinomatous cells had invaded the Virchow-Robin spaces of several small vessels (fig. 13). Aside from these, selected sections from the brain stem showed mild degenerative changes in the parenchyma.

General Necropsy Observations.—Primary papillary adenocarcinoma of the adrenal gland was observed, with metastasis to both lungs.

In this case the cerebral manifestations appeared late in the clinical course. It is not improbable that the disseminated and microscopic character of the metastatic lesions was responsible for the rapidity with which the fatal issue took place. The lesions and their distribution were not unlike those seen in cases of diffuse encephalopathy.

CASE 21.—*History of loss of weight for seven months and vague generalized pains. Appendectomy. Lump in the submaxillary region. No neurologic signs. Roentgenographic evidence of a malignant process in the ribs and spine. Biopsy showed the cervical gland to be the seat of the metastatic adenocarcinoma. Pathologic fracture of rib; terminal bronchopneumonia; death one month after admission. Necropsy: primary carcinoma of the lung, with generalized metastases, including the foci in the brain.*

History.—A man aged 35 years was first studied in the medical service of the hospital. He had apparently been well until seven months before admission, on Jan. 15, 1937, when, while exercising, he suddenly experienced a sharp pain in the right lower posterior portion of the chest and the right loin. The pain recurred several times, and two months later an appendectomy was performed for its relief. After the operation he began to have pains in the left side of the chest, and a productive cough developed. The pains in the right groin spread to the right thigh. Pain in the back of the neck, flushing and excessive perspiration, especially at night, followed. One week before admission he noted a nontender lump in the right submaxillary region. During the seven months of his illness he had lost about 35 pounds (15.9 Kg.) in weight.

Examination.—Neurologic examination revealed nothing abnormal. The blood pressure was 110 systolic and 72 diastolic. The prostate was hard and nodular. There was a subcutaneous nodule at the upper end of the right sternocleidomastoid muscle. The lungs were normal.

Laboratory Data.—Roentgenograms of the lungs and skull were reported as normal; roentgen examination of the spine showed some areas of rarefaction in the sixth dorsal vertebra and the fourth, tenth and eleventh ribs, raising the suspicion of a malignant growth. Examination of the blood and urine gave normal results.

Course.—A diagnosis of carcinoma of the prostate gland with multiple metatases to the spine was suggested. The subcutaneous nodule in the neck was excised and was reported as containing adenocarcinoma of the mucous cell type. It was then thought that the primary site was in the respiratory tract. The patient's

condition declined; a pathologic fracture of the sixth right rib took place (February 3), accompanied by a cough with bloody sputum. Dulness on percussion developed in the upper lobe of the left lung. Death occurred at the end of four weeks in the hospital.

Necropsy.—Gross Anatomic Changes: On sectioning the brain, a small well circumscribed, slightly hemorrhagic area, measuring ¼ inch (6 mm.) in diameter, was seen in the right temporal lobe. In the left temporal lobe there was a small area of softening in the cortex of the second temporal gyrus. A third lesion was noted on the ventral aspect of the left temporal lobe. This measured ¼ inch in diameter and was well circumscribed, with a greenish, gelatinous appearance.

Microscopic Observations: Sections of one of the tumor masses showed the cells to be arranged in an acinous or papillomatous formation. The stroma of connective tissue serving as the core of the villus-like projections was thin and contained thin-walled blood vessels. For the most part, one layer of neoplastic cells formed the lining of the acini. The cells were columnar, and their small, round or oval nuclei were situated at the base of the cells. The acini contained mucus-like material and often desquamated tumor cells.

A second nodule showed a variant of this microscopic picture. Here, the acinous and papillomatous formations were infrequent. Instead, large masses of neoplastic cells of the squamous epithelial type were seen. They varied considerably in size and shape. Their nuclei, which were moderately chromatinized, showed even greater variation. Many were grotesque, lobulated and heavily chromatinized, and in some cells several nuclei were present.

General Necropsy Observations.—Primary carcinoma of the mucous cell type was found in the lower lobe of the left lung, with extensive metastases to the abdominal and thoracic organs.

The relatively small size of the lesions, their distribution in relatively silent areas of the brain and their probable recent development provide the likely explanation for the absence of neurologic signs.

SUMMARY OF CLINICAL OBSERVATIONS

Age and Sex Incidence.—The majority (42 out of 57) of the cases in this series occurred between the ages of 30 and 60, as the following tabulation indicates. This age incidence curve parallels that of malignant tumors in other organs, particularly those primary in the respiratory tract.

Age Yr.	Number of Cases
0- 9	1
10-19	1
20-29	3
30-39	9
40-49	16
50-59	17
60-69	8
70-79	2

An unusual observation was the occurrence of the cerebral metastases in 38 males as against 19 females, a proportion of exactly 2:1. This ratio was maintained almost within each decade, but for circumstances

peculiar to this hospital, our series contains only 1 case in which the primary lesion was in the breast, a situation which may well explain the preponderance of metastases in men in our series.

Prodromal Events.—Aside from complaints referable to the chest, such as cough and dyspnea, and loss of weight, the clinical manifestations noted in the past history of the patients were not particularly informative. In none of the cases was there recorded any complaint of a symptomatic character for more than one year prior to admission into the hospital. A complaint of some pulmonary disturbance was elicited in 26 per cent of the cases and consisted in all but 1 case of cough, often productive, the sputum occasionally being stained with blood. Dyspnea was another complaint in 5 cases.

Loss of weight was a conspicuous sign in 37 per cent of the cases. The patients' estimate of the loss in weight varied from 8 to 38 pounds (3.6 to 17.2 Kg.), the average being computed to be 24 pounds (10.9 Kg.). In 1 instance there was, however, a gain of 20 pounds (9.1 Kg.) in the course of three months prior to admission.

Other symptoms which marked the history of the patient were variable in degree and constancy and included headache of years' standing in a few cases; pain in various parts of the body in another group (7 cases) and isolated symptoms, such as bilious attacks, grip, periods of weakness, visual disturbances, palpitation, nocturia, anorexia, constipation, drowsiness and tarry stools, in various constellations in other cases.

Mode of Onset.—A history of sudden onset of the neurologic complaints was given in 38 cases and of gradual development in 11 cases; the history was not clear on this point in 3 instances, while in the remaining few cases no neurologic complaints were recorded, the metastatic lesion having been discovered only at autopsy.

Symptoms.—The most frequent and prominent symptom marking the onset was recurrent headache (14 cases), accompanied in several instances by vomiting and vertigo. Hemiparesis or hemiplegia appeared at the onset in 8 cases. Diplopia or dimness of vision was reported in 4 cases. Mental changes in the early stage of the illness appeared in 5 cases. Pain of various types, distribution and intensity was an early symptom in a few cases, in which, with few exceptions, it had little bearing on the clinical picture. Convulsive seizures ushered in the fatal clinical course in 2 instances.

Signs of Intracranial Tension.—Papilledema was absent in a large number of instances (34 cases), moderate in some (16 cases) and pronounced in only a few (7 cases). Headache, vomiting and dizziness, as already mentioned, were early symptoms and were also present at the height of the clinical course in a fairly large number of instances. But while the headache and its accompanying symptoms manifested them-

selves early in the course of the disease and were intense in degree, the papilledema was comparatively mild and progressed slowly and out of tempo with the evolution of other clinical signs.

Signs of Meningeal Irritation.—Such indications of meningeal involvement as rigidity of the neck or the Kernig sign were not outspoken, certainly not to a degree noted in cases of meningitis of bacterial origin. The presence or absence of meningeal signs does not seem to bear any relation to the proximity of the metastatic tumor to the surface of the brain.

Mental Disturbances.—Mental alterations were found somewhat more frequently (23 cases) than are usually encountered in cases of primary tumor of the brain. In about half the number these disturbances had already existed for a brief period before the patient's admission to the hospital. In practically all cases the mental changes were noted at the time of admission. They usually continued and in some instances became more severe in the later part of the course. These psychic alterations varied considerably: in some patients indifference to their surroundings; in others changes in personality; in still others confusion and disorientation, while impairment of memory was a fairly constant feature. In only 1 case were there ideas of persecution, and then they appeared only on the day of admission. The mental states of these patients were variously described as dull, confused, rambling, disoriented, irrational, delirious or euphoric, irritable, unstable and restless.

The mental symptoms did not appear to bear any relation to the character, anatomic distribution or number of the metastatic lesions, which were either single or multiple and were present in any part of the cerebrum and cerebellum.

Involvement of the Cranial Nerves.—Signs pointing to probable implication of the cranial nerves were noted in 40 cases. The facial nerve (peripheral portion) was affected in the great majority of instances (29 cases). In general, the degree of involvement was slight. In 2 cases there was absence of the sense of taste. The sixth nerve was involved in 11 instances, in some bilaterally. The fifth nerve showed some disturbance in 9 cases, and this generally took the form of diminution or absence of corneal sensibility, while in a few instances hypesthesia of the side of the face appeared. Differences in the size of the pupils, sluggish reactions to light and in accommodation and suggestions of ptosis were evident in a large number of instances.

Other Neurologic Signs and Symptoms.—These included hemiparesis, in 14 cases; aphasia, in 4 cases; nystagmus, in 7 cases, and signs of incoordination, in 6 cases.

Laboratory Data.—Studies of the cerebrospinal fluid contributed little to the diagnosis. While the cell count in the cerebrospinal fluid was

at times somewhat elevated, and occasionally even very high, in no case were tumor cells discovered. An increase in the globulin and a slight increase in sugar in the cerebrospinal fluid noted in a few cases could not, of course, be regarded as suggestive of metastatic disease.

Studies of the blood and urine did not reveal any significant data.

Test meals were given in a number of cases and revealed the absence of free hydrochloric acid in 4 instances, in 3 of which permission for complete necropsy was obtained. In 2 of these the stomach was free from pathologic changes; in 1 metastatic carcinomatous tissue was noted in the wall of the stomach. In an additional case, however, in which carcinoma of the stomach was revealed at necropsy, the test meal revealed normal quantities of free and combined hydrochloric acid.

Evolution of the Clinical Course.—The clinical course was marked by a sharp termination of the early stage, in which the signs of cerebral involvement were vague, and by an almost precipitate onset of manifestations resulting from focal disease of the brain. In a large number of instances these symptoms pointed to the presence of a single circumscribed lesion. A rapid turn in the clinical picture was usually marked by an equally rapid decline in the general condition of the patient.

Duration of the Disease.—The duration of the clinical course from the onset of illness to death varied from one day to two years and seven months, the average period being four months. In the great majority of cases, however, the interval from onset to death was from three to six months. The period from the onset of the neurologic symptoms until the time the patient was admitted to the hospital was on the average two and a half months, the extremes being one day and nine and a half months. In general, the symptoms of cerebral involvement had existed less than four months at the time of admission. The average stay in the hospital in cases of metastatic neoplasms was only one and four-tenths months. These periods differed somewhat in instances in which the metastatic foci in the brain were multiple. In such cases the average interval from onset to death was only three and two-tenths months, a period slightly lower than the general average. Slight differences in the interval from onset to death were also found on the analysis of figures with respect to the organ harboring the primary focus, but these differences were not large enough to warrant their presentation.

Surgical intervention for the removal of the cerebral neoplasm lengthened slightly the interval from onset to death in a few selected cases considerably.

Non-Neurologic Symptoms.—When one is in search of a correct diagnosis of a metastatic cerebral neoplasm, the symptoms and signs referable to organs other than the brain and signs which serve as an index to the general condition of the patient are exceedingly important. This, of course, is obvious when it is realized that a patient with a

metastatic process in the brain harbors a malignant neoplasm elsewhere and that such a growth ultimately leads to a general decline in the patient's condition, with the loss of weight, strength, etc., even before the function of the invaded brain is disturbed. Recognition of these general and local symptoms in a patient who is displaying evidence of intracranial tension will often lead to the correct diagnosis of an intracranial metastatic growth.

General Observations.—The condition of the patient was variously described as chronically ill, wasted, pallid, cachectic, emaciated or poorly nourished in nearly half the cases, thus providing evidence for the presence of an underlying malignant disease.

Mild secondary anemia was found in only an occasional case. The blood pressure readings showed a tendency to be in the range of "low normal" or "subnormal." Of greater significance were the symptoms and signs pointing more definitely to implication of organs other than the brain.

Lungs: The lungs were foremost in the frequency with which they disclosed symptoms and signs indicating involvement. In 26 instances in which a diagnosis of carcinoma of the lungs was made some evidence of its existence was found either in the history or on physical examination of the patient. In many instances the signs elicited on examination of the chest were sufficiently severe to indicate serious implication, and in cases in which roentgen studies were carried out a diagnosis of a malignant process could be definitely made. In only a few instances did roentgen studies fail to reveal such a process. In no case in which the primary focus was in the lung were symptoms suggestive of pulmonary involvement absent. In only 3 instances in which the lungs were the seat of metastatic deposits was there complete absence of signs pointing to their presence there. The importance of symptoms pertaining to the chest in relation to probable intracranial metastasis is obvious when it is noted that in 83 per cent of cases in this series in which full anatomic investigation was made the lungs were affected, either as the seat of the primary lesion or as the site of metastasis.

Not without interest are the roentgenologic data pertaining to the chest. Of those cases in which the autopsy included an examination of the chest, there were 20 in which roentgenographic studies were made. In 9 such instances the existence of carcinoma in the lungs was recognized, and in all of these the roentgenographic diagnosis was confirmed at autopsy. In 3 instances a "suspicious shadow" was reported, in all of which postmortem examination revealed a carcinoma of the lungs. In the remaining 8 cases no roentgenographic evidence was reported. Of this group, autopsy revealed the presence of a neoplasm in the lung in 7 instances. In only 1 case did autopsy fail to disclose carcinoma.

Stomach: Symptoms referable to this organ were present in 5 instances; but in only 2 was the stomach found to be the seat of a malig-

nant process. The fractional test meal was reported as normal in 1 case; in the other there was no free hydrochloric acid. On the other hand, in another case in which no malignant growth was found a test meal did not reveal any free hydrochloric acid.

Prostate: In 3 cases the prostate was hard and nodular or enlarged. In 1 of these cases a primary carcinoma was found; in another, a metastatic carcinoma, and in the third the gland was free of tumor growth.

Liver: The liver was found to be enlarged in 5 instances. Postmortem examination revealed carcinoma in 3 other cases; strikingly enough, in these 3 instances enlargement of the liver was not noted on physical examination.

Thyroid: This organ was enlarged and hard in 3 cases, and in each a carcinoma was present.

Abdomen: Palpable masses were discovered in 2 cases; in both instances there was generalized carcinomatosis.

Spleen: Aside from being found enlarged during life in 1 case, in 2 instances this organ was noted at autopsy to be the seat of metastatic nodules, without detectable enlargement during life.

Intestinal Tract: Blood was detected in the stools in 2 cases; in 1 a carcinoma of the rectum and in the other a carcinoma of the stomach was present. In a third instance rectal examination revealed a hard mass, which proved at autopsy to be a carcinoma. In a fourth case obstinate constipation set in while the patient was in the hospital; autopsy disclosed a carcinoma of the sigmoid portion of the colon. In a fifth case a carcinoma of the sigmoid part of the colon, unsuspected during life, was observed at autopsy.

TRAUMA IN RELATION TO METASTATIC TUMOR OF THE BRAIN

The role which trauma plays in initiating the growth of a neoplasm, in the acceleration of such growth or in the determination of sites for metastasis is the subject of considerable discussion. In only 5 cases in this series was a history of definite injury elicited. In 3 cases the injury antedated the onset of neurologic symptoms by two to five months; thus, the probability that there existed a relation between the trauma and the subsequent clinical manifestations was considerably reduced.

The following 2 cases are presented to illustrate points related to this problem.

CASE A (case 14 in this series).—A man aged 44 sustained a blow to the left eye during a street fight. He made an uneventful recovery, but two months afterward hoarseness suddenly developed, followed by dimness of vision. Postmortem examination disclosed an adenocarcinoma, primary in the right lung with infiltrative metastases to the brain stem, the spinal cord and the left optic nerve. While the question will be raised whether the blow to the eye with sub-

sequent carcinomatous infiltration in the left optic nerve can be dismissed as a mere coincidence, it may be pointed out that the period of two months elapsing between the time of the trauma and the initial neurologic complaint and the even greater lapse of time before dimness of vision appeared speak against the probability of the trauma's being a contributing factor.

CASE B (case 8 in this series).—A man aged 53 was injured when a man fell on his head from a height of 20 feet (6 meters). He was thrown to the ground and lost consciousness for about thirty minutes. Headache followed and persisted for one week. On returning to work a few days later, he found himself unable to perform his duties as rapidly as previously because of blurred vision; reading caused headache. At the end of two months he became aware of memory defects and occasional confusion. This was followed by difficulty in walking.

Necropsy disclosed a large metastatic neoplasm in the right occipital lobe. Here, again, it may be held that the injury to the head initiated the train of neurologic symptoms leading to the fatal outcome. More direct proof to support such an assumption is required before the causal relation between the trauma and the subsequent fatal event is established.

The effect of the trauma on the organs harboring the primary focus cannot be deduced from the cases in this series, since in only 2 of the 5 cases in which a history of trauma was elicited was complete postmortem examination performed.

Of significance is an observation made in 4 cases which were characterized by the presence of miliary microscopic lesions. In 2 of these there was a history of trauma, but in both instances periods of two and a half months and five months, respectively, elapsed between the time of the injury and the onset of the neurologic symptoms. This, together with the character and mode of development of the lesions, argues against a causal relation between the violence in question and the cerebral lesion.

ANATOMIC CONSIDERATIONS

Distribution.—The anatomic grouping of the cases in the material under investigation is a much simpler problem, although it is of necessity arbitrary. Thus, in the first category, which included 22 cases, or 38.6 per cent of the total number, the tumor was *single*, most often spherical and usually large, measuring from 2.5 to 4 cm. in the longest diameter. It was more commonly located in the cerebral hemisphere, without favoring any particular side or subdivision, but often also invaded brain structures in the posterior fossa. In 4 cases the growth was limited to the frontal lobe, while in 2 cases it was found in the parietal lobe, in 1 in the temporal lobe and in 3 in the occipital lobe. In 5 cases the tumor was situated at the junction of the parietal and an adjacent lobe of the hemisphere. The cerebellum was the seat of metastatic growth in only 2 instances. In 4 cases the metastatic focus was at the base of the brain and infiltrated the cranial nerves. In 1 case the left lateral ventricle was the site of a metastatic melanocarcinoma.

In a second, and larger, group, which included 30 cases, or 52.6 per cent of the total number, the tumors were multiple, disseminated and variable in number, size and distribution. In general, the lesions in this group tended to be considerably smaller than did the single metastatic tumors. This was probably due to the fact that in instances of multiple lesions the growth period is shortened by the more rapid fatal issue. The average tumor was about 1 cm. in the longest diameter, and only in the exceptional case did one measure as much as 4 to 5 cm., while the smallest lesion measured only a few millimeters. No part of the cerebral

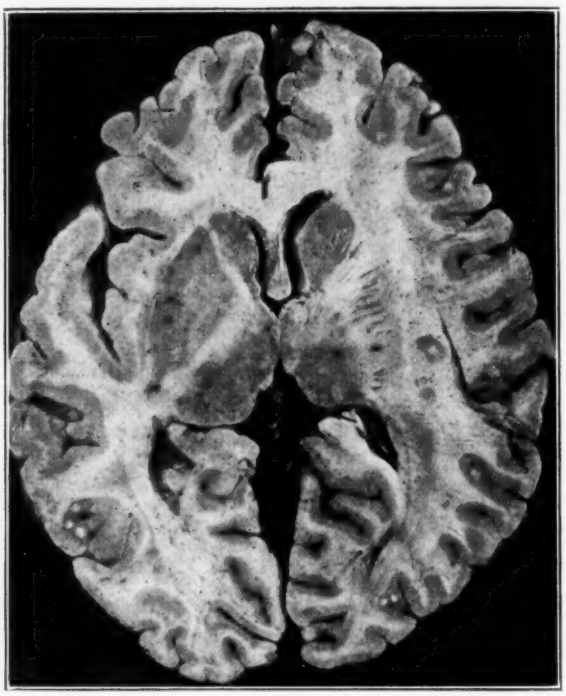

Fig. 14.—Gross appearance of the so-called miliary metastatic deposits.

or cerebellar hemispheres was apparently exempt, and in a few cases the brain stem and the cranial nerves were also invaded. Occasionally the lesions had a symmetric bilateral distribution (fig. 10*A*), simulating bilateral acoustic neuroma.

No correlation could be found between the distribution of metastases and a particular cerebral blood vessel, although the impression was gained that the territory supplied by the middle cerebral artery is a more common seat of metastases. This, however, is probably explained by the fact that this artery supplies a relatively large cerebral territory. Finally, there were a few instances in which deposits were observed also

in the calvarium, the dura mater, the spinal cord and the dorsal and lumbar vertebrae as part of the generalized metastasis.

In the third, and relatively smaller, group, constituting 8.8 per cent (5) of the total number of cases, the metastasis was of the character of a diffuse infiltration. In 2 cases of this type no gross evidence of tumor could be seen, and the metastatic deposits were detected only on microscopic examination (fig. 13). In the 3 remaining cases small lesions were grossly visible. These measured a maximum of but a few millimeters in diameter (fig. 14). The microscopic study also revealed carcinomatous cells in the leptomeninges.

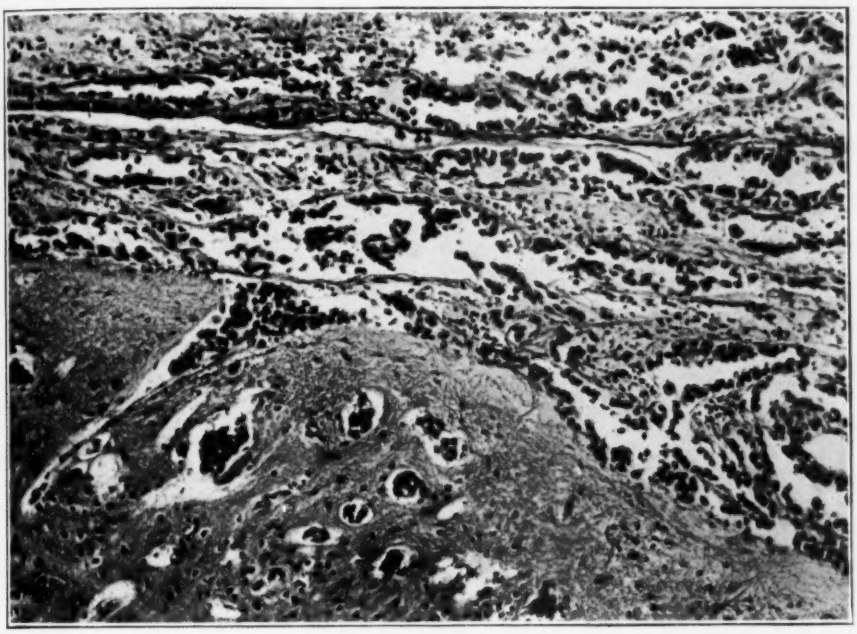

Fig. 15.—Section of cerebral cortex and overlying meninges, showing carcinomatous invasion of the pia-arachnoid and extension into the cerebral cortex by the perivascular route. × 105.

In a few instances tumors were restricted to the dura and in 1 case to the leptomeninges (fig. 15).

Character of the Metastatic Tumors.—In the great majority of the cases in this series (49 out of 57) the lesion was of a type usually described as carcinoma, while the rest consisted of 2 instances of the Grawitz tumor and 1 instance each of neuroblastoma, lymphosarcoma, spindle cell sarcoma, melanosarcoma, chorionepithelioma and Ewing's sarcoma. The high incidence of carcinomatous metastasis is accounted for by the greater frequency of this type of growth in the primary site,

and particularly by the frequency with which carcinoma of the lungs is likely to metastasize to the brain. At this point, it may be emphasized that whether the lung is the seat of a primary carcinoma or the site of a metastasis from a primary focus elsewhere, the probability of demonstrating there a malignant focus by roentgen examination or other means in the presence of metastasis to the brain is rather great. This observation is supported by our material, in which in nearly all of the 33 cases in which a complete necropsy was done the examination disclosed either primary or secondary neoplasm in the lung.

Seat of the Primary Lesion.—In the 33 cases of carcinoma in which complete autopsy was performed, the following distribution of the primary lesion was noted:

Primary Seat	No. of Cases
Lungs	19
Thyroid	4
Rectum	3
Sigmoid	2
Stomach	1
Adrenal glands	1
Kidneys	1
Prostate	1
Unknown	1

In addition, there were 3 cases in which complete autopsy was not done but in which an operative procedure indicated clearly the seat of the primary lesion: In 1 case it was a carcinoma in the breast, in another a pigmented mole in the left leg and in still another a small melanotic tumor in the skin of the right foot.

In the small group of cases of a tumor other than carcinoma the primary sites were as follows:

Primary Site	No. of Cases	Type of Tumor
Adrenal	2	Grawitz
Left femur	1	Ewing
Bladder (urinary)	1	Chorionepithelioma
Skin (neck)	1	Melanosarcoma

Distribution of Metastases to Other Organs.—In all the cases in which a full postmortem examination was performed, metastasis to the brain was found to be but an expression of generalized metastasis, as revealed by inspection of other organs into which dissemination of the new growth had taken place. The lungs, when not the primary focus of the malignant disease, were free of recognizable metastatic foci in only 6 cases. In 7 of the 24 cases in which autopsy was limited to the brain but the chest was examined roentgenographically, the presence of metastases in the lungs was detected. In a survey of the protocols of the cases

of metastatic cerebral tumor in which complete necropsy was performed, it was found that other organs were invaded with the following frequency: adrenal glands, 36 per cent; liver, 28 per cent; kidneys, 22 per cent; long bones, 22 per cent; heart, 17 per cent; lymph glands, 17

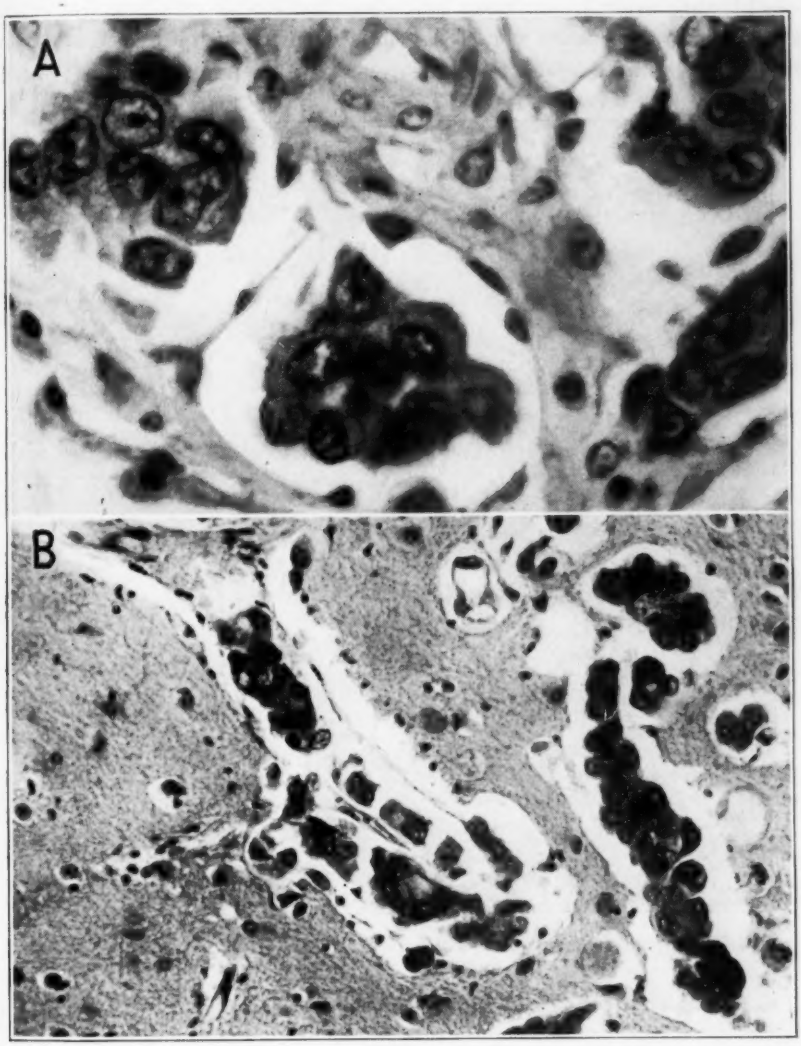

Fig. 16.—*A*, tumor cells in perivascular space; the vessel wall is no longer discernible. × 625.

B, tumor cells in capillary and in the perivascular space (see figure 14). × 225.

per cent; pancreas, 8 per cent, and spleen, 5 per cent. The pelvis, skin and prostate were infrequently involved as secondary seats of metastasis.

Spread of Metastatic Foci in the Brain.—Extension of a metastatic tumor appears to take place by way of perivascular spaces (fig. 16) and occasionally by actual transportation of small cell groups through the vascular channels (fig. 17). With the vessels so occluded, necrosis of neighboring brain tissue takes place and the tumor cells are deposited as islands in these areas (fig. 18). This is borne out by the observation that the adventitial spaces of blood vessels in the parenchyma adjoining

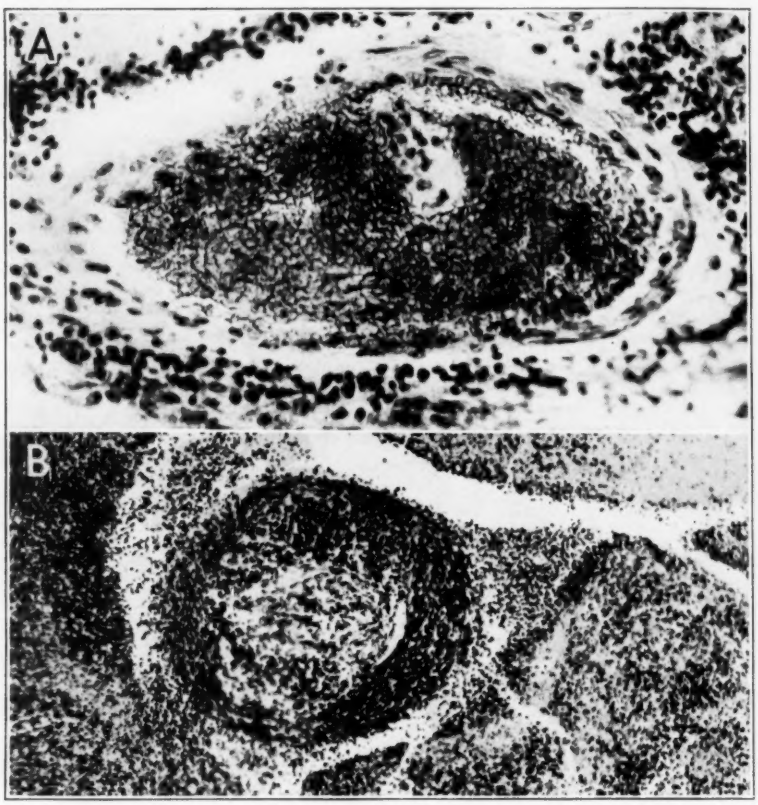

Fig. 17.—*A*, vessel carrying a small group of tumor cells in its blood stream. × 275.

B, vessel almost completely occluded by tumor cells. × 97.

the metastatic mass are packed with tumor cells. Since these spaces are but a part of the system through which the cerebrospinal fluid circulates, they serve as a free pathway for the dissemination of the metastatic cell elements. Moreover, since these channels open into the subarachnoid space, invasion of that space from contiguous cortical areas is not infre-

quent (fig. 19 *A*). Then, again, metastatic nodules may reach the periphery of the area of the affected part of the brain without breaking into the subarachnoid space (fig. 19 *B*). More common, however, are extensions from carcinomatous areas in the meninges into the underlying cortex (fig. 20).

Transportation of Tumor Cells to the Brain.—Evidence favors the blood stream as the main channel of transportation of tumor cells from other parts of the organism. Fried,[6] in a study of primary carcinoma of the lungs with intracranial metastasis, came to the same conclusion.

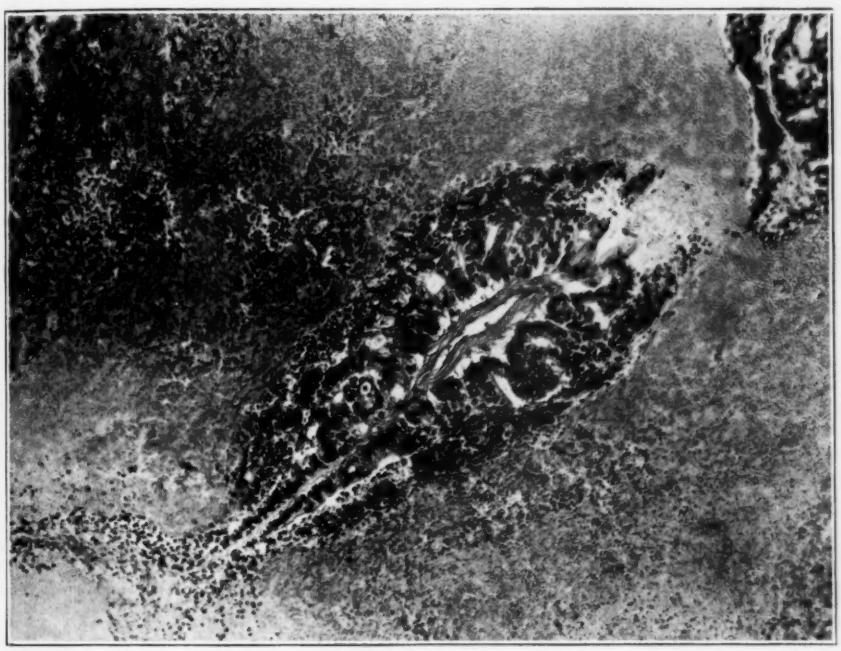

Fig. 18.—Vessel the perivascular space of which is filled with tumor cells. It is surrounded by a wide zone of necrobiosis. × 70.

Although it may be accepted that the initial metastatic focus finds its way into the brain with the blood stream, it is only in rare instances that one can find a blood vessel plugged with neoplastic cells. This difficulty is due to the rapidity with which the tumor cells destroy the vessel which harbors them, leaving practically no trace of it in an area now occupied by tumor cells and necrotic tissue.

Mention is often made of the probability that lymphatics may serve as channels for the transportation of tumor cells to the brain. In such dis-

6. Fried, B. M.: Primary Carcinoma of the Lungs, Baltimore, Williams & Wilkins Company, 1932.

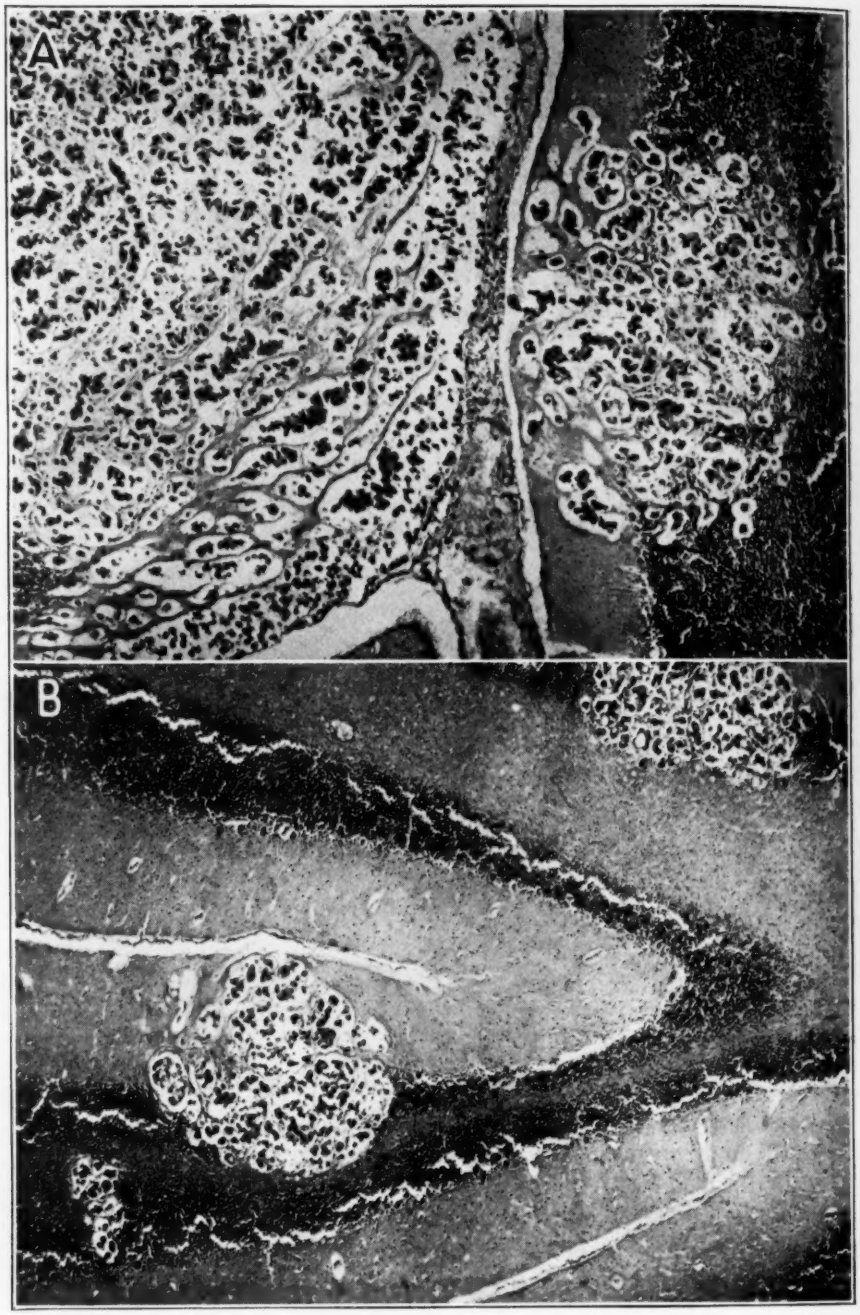

Fig. 19.—*A*, section of the cerebellum, showing extension of the metastatic lesion into the overlying leptomeninges. × 53.

B, section of the cerebellum, showing metastatic nodules which approach the surface without breaking into the subarachnoid space. × 48.

cussions no clear distinction is made between the perivascular system of Virchow and Robin and true lymphatics. Certainly, these two systems are independent in the main and are not to be confused. The former is an extension of the subarachnoid (pia-arachnoid) space and serves as a channel for the passage of cerebrospinal fluid and, because of that, as an intramural channel for the spread of the metastatic focus as well. It is, nevertheless, not a part of the true lymphatic system. On the other hand, consideration must be given to the views concerned with the existence of the lymphatics in the nervous system. Mascagni [7] stated that true

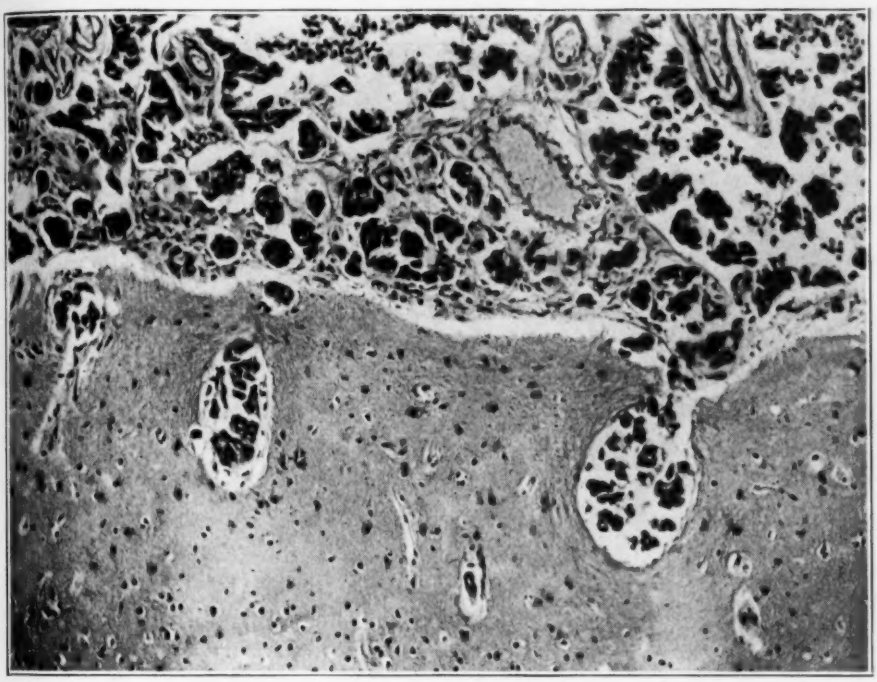

Fig. 20.—Section of cerebral cortex, showing carcinomatous cells in the subarachnoid space, extending into the cortex by way of the perivascular spaces. × 105.

lymphatic vessels are present along the middle cerebral, inferior cerebellar and vertebral arteries. Fohmann [8] and Arnold,[9] by methods of injection, described a lymphatic network in the pia mater "connected with the

7. Mascagni, P.: Vasorum lymphaticorum corporis humani, Senis, ex. typog. P. Carli, 1787.

8. Fohmann, V.: Mémoire sur les vaisseaux lymphatiques de la peau, des membranes muqueuses, séreuses, du tissu nerveux et musculaire, Liége, J. Desoer, 1833.

9. Arnold, F.: Lymphgefässe des Gehirns, in Tabulae anatomicae, Turin, imp. Orellii, Fuesslini et sociorum, 1838, pt. 1.

circulation." The dura mater is also said to have some spaces continuous in part with lymph vessels, which commence "on the external surface of the dura" and reach neighboring lymph nodes. In this connection it may be recalled that Hassin,[10] studying cerebral metastasis of carcinoma of the breast, suggested the passage of the tumor cells from the primary seat to the meninges by way of perineural spaces. He expressed the belief that at first the neoplastic cells enter the lymphatics, reach the lymph vessels of the neck and then by way of tissue spaces find access to perineural spaces. There, they "climb" upstream to enter the meninges and in this way may reach the brain. In our material we

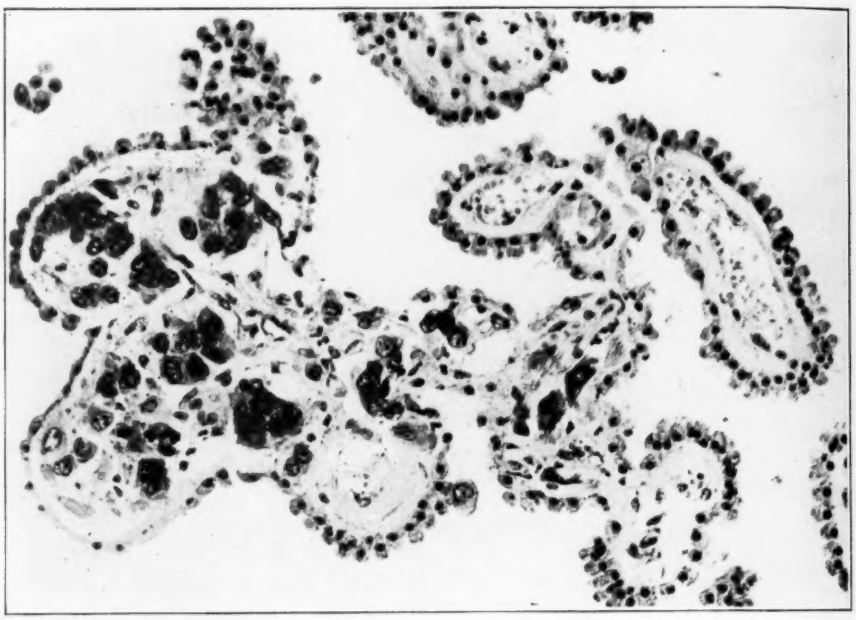

Fig. 21.—Section of the choroid plexus, showing carcinomatous cells within the blood vessels. × 150.

found little evidence to support the existence of such channels or their probable service as channels for the transportation of neoplastic cells. We have among our cases only 2 of metastasis to the dura and 4 of initial spread to the leptomeninges.

A study of the choroid plexus with a view to determining its role in the transportation of tumor cells to the nervous system gave disappointing results. In only 1 instance was this structure the seat of metastasis (fig. 21), and this was in a case in which great numbers of miliary carcinomas were distributed throughout the brain.

10. Hassin, G. B.: Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. **1**:705 (June) 1919.

Behavior of Metastatic Tumors in the Brain.—The tumor tissue itself, consisting, as it does, of a conglomeration of islands of metastatic cells in a large area of necrosis, is usually rich in blood vessels and occasionally shows extravasation into the relatively large areas of necrobiosis. A fairly large number of such tumors contain cysts filled with gelatinous material (fig. 6). These cysts are generally sufficiently large to be obvious to the unaided eye. Frequently the metastatic lesion is composed almost entirely of such gelatinous substance, and only after careful search is a small zone of neoplastic tissue found. In a small group of

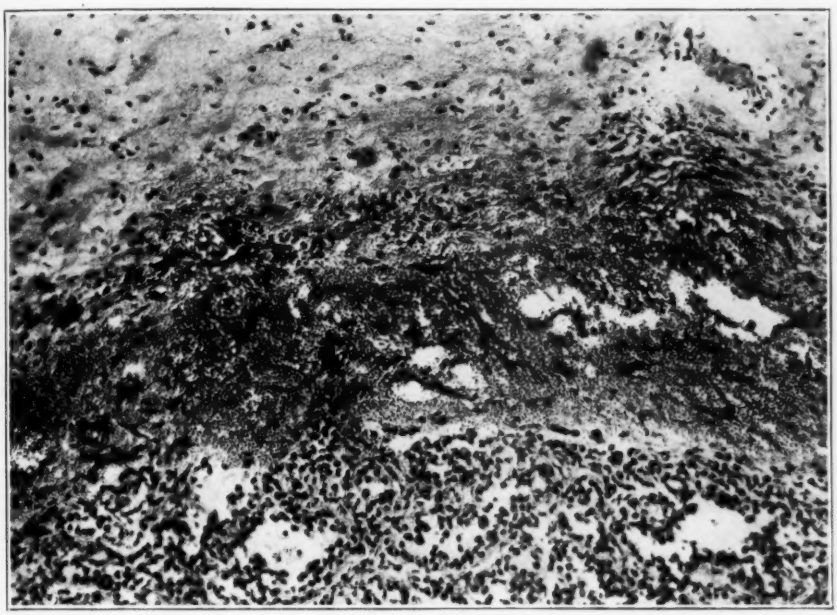

Fig. 22.—Section of the metastatic nodule (Grawitz) tumor, showing a zone of hemorrhage. × 90.

instances the metastatic invasion of the brain is widespread and miliary (fig. 14). The metastatic foci are in some instances restricted to small zones about blood vessels and are occasionally recognized only on microscopic examination (fig. 13).

Reaction of Brain Tissue to Metastases.—It seems that the growth of a metastatic tumor takes place at the expense of adjacent brain tissue,[11] but in spite of this invasive character, a discrete line of demarcation between the tumor and the better preserved adjacent tissue is often

11. Hassin, G. B., and Singer, H. D.: Histopathology of Cerebral Carcinoma, Arch. Neurol. & Psychiat. **8**:155 (Aug.) 1922.

maintained and only mild reactive changes, such as a narrow zone of tissue of condensation, gliosis and occasional lymphocytic infiltration in nearby brain tissue, are present. The glial alterations consist not only of an increase in the number of cells but of a change into hypertrophied and "fattened" forms, with numerous interlacing and prominent processes. Such hypertrophied glia cells are easily detected even in sections stained by routine laboratory methods and are most numerous in areas adjacent to the metastatic focus. The somewhat more remote brain tissue commonly shows wide areas of edema, which occasionally extend for a considerable distance into the adjacent tissue.

Nerve cells in the proximity of a metastatic focus exhibit varying degrees of degenerative alteration. Such changes are nonspecific and give no indication as to the underlying disease process.

The blood vessels in the proximity of a metastatic lesion show moderate congestion and in rare instances a narrow zone of hemorrhage about the neoplastic center. This is particularly true of metastatic nodules from the more primitive, the so-called Grawitz, type of tumor, or hypernephroma (fig. 22).

Histologic Comparison of the Metastatic Lesion and the Primary Tumor.—Frequently the pathologist is presented with a small fragment of tissue obtained at an exploratory craniotomy and is called on not only to recognize it as a metastatic lesion but to identify its primary source. This is a difficult task and only rarely is met with success. It was thought, therefore, that it would be useful to review the available sections of the primary lesion and to compare their histologic appearance with that of the secondary lesions in the brain. This study was carried out by observations on routine material, and some conclusions were drawn. It was found that the histologic structure of tumors primary in the lung is often duplicated by that of the secondary masses in the brain. Not infrequently the structure of the metastatic focus in the brain is more characteristic than that of the primary lesion in the lung (fig. 23). On the other hand, still more infrequently its structure deviates notably from that of the primary focus and the tumor cannot be identified. The same is true of the Grawitz tumor and tumors arising in the gastrointestinal tract. Occasionally a primary carcinoma of the thyroid may be well simulated by the secondary mass in the brain. This is all that can be said with the material at hand. It may be added that a careful biopsy should lead one to a correct diagnosis of the metastatic nature of the lesion. It may often reward one with the disclosure of the primary seat, but more often there will be disappointment in this respect.

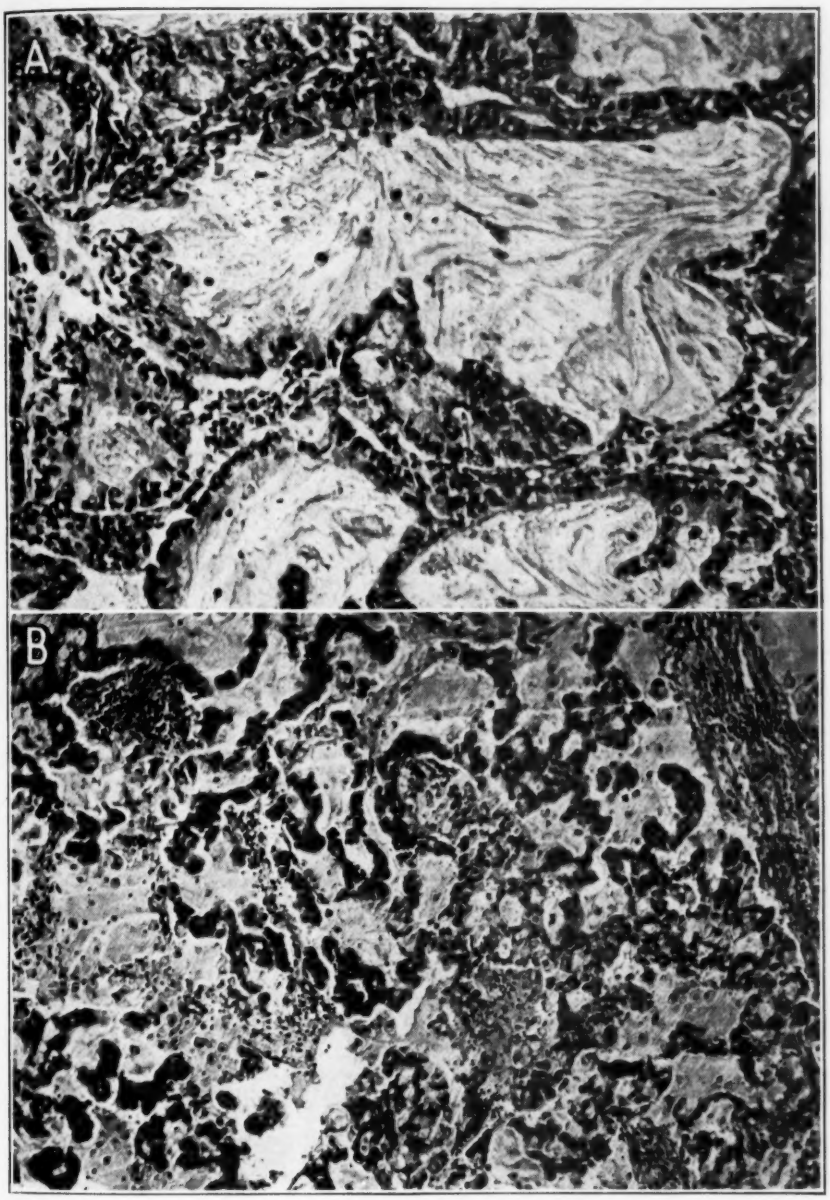

Fig. 23.—*A*, section of a metastatic cerebral tumor. × 201.

B, section of the primary lesion (carcinoma in the left upper bronchus) in the same case. × 90.

SUMMARY AND CONCLUSIONS

The clinical manifestations and the anatomic observations in 57 cases of metastatic tumor of the brain are analyzed.

A. On the clinical side, observations on the evolution of the symptoms and signs in cases of metastatic tumor of the brain point to the following conclusions:

The onset of cerebral manifestations is most commonly acute and often precipitate, with symptoms of increased intracranial tension, such as headache, nausea and vomiting. These symptoms, appearing early in the disease, manifest themselves in an intensity out of proportion to the then present meager objective neurologic signs.

Papilledema is absent in a large number of instances (34 cases, or 59.6 per cent, in this series); moderate in some (16 cases, or 28 per cent), and pronounced only in a few (7 cases, or 12 per cent).

The presence or absence of meningeal signs does not seem to bear any relation to the position of the tumor in the brain.

Mental alterations are found in a somewhat greater number of cases of metastatic than of primary tumor of the brain (23 cases in this series).

The evolution of the clinical course is characterized by a rapid transition from the early stage, in which the cerebral signs are few and vague, to a stage in which manifestations of an existing focal lesion of the brain are prominent. In a large number of instances these may be of a disseminated character, and in an equal number of instances they may point to the presence of a single circumscribed process. The rapid unfolding of the clinical picture is marked by an equally rapid decline in the general condition of the patient.

The laboratory investigations pertaining to the cerebrospinal fluid contribute little to the diagnosis. While the cell count of the cerebrospinal fluid at times may be above normal, or even very high, tumor cells are rarely discovered in the fluid. The increase in the globulin and the slight increase in the sugar content of the cerebrospinal fluid noted in a few cases are not pathognomonic of metastasis.

Thus, it may be said that an acute onset of symptoms of increased intracranial tension, such as headache and vomiting, followed by rapidly progressive development of neurologic signs of either disseminated or more localized character, accompanied by slow development of papilledema in the absence of positive serologic reactions and febrile manifestations, points strongly to an expanding lesion of a metastatic character. Such a suspicion demands search for a primary lesion by all available clinical and laboratory methods, since the therapeutic indications depend on recognition of the character of the neoplastic process.

In some instances the knowledge thus obtained may point to the advisability of intracranial surgical intervention, with promise in some

instances of temporary relief from the more disabling and painful symptoms and prolongation of life, and in rare instances still better results. Surgical treatment was attempted in a limited number of cases in this series. In some cases this was done because the metastatic character of the lesion was not recognized. The result of successful removal of the tumor somewhat lengthened life with comfort beyond the probable life expectancy.

B. The anatomic features may be summarized as follows:

In the larger number of cases (52.6 per cent of the total series) multiple tumors, variable in size and distribution, were revealed, while in a somewhat smaller group (38.6 per cent) the metastatic lesion was single and massive. Finally, there was a third, very small, group, constituting 8.8 per cent of the total number, characterized by diffuse, microscopic infiltrations. The great majority of the tumors in this series were observed in the brain substance. Only in 1 case was the lesion restricted to the dura and in 1 case to the leptomeninges.

In 49 of the 57 cases the metastatic lesion was in the nature of a carcinoma, leaving only 8 cases to be distributed among tumors of other types; the Grawitz tumor (2 cases) and neuroblastoma, lymphosarcoma, spindle cell sarcoma, melanosarcoma, chorionepithelioma and Ewing's sarcoma (1 case each). This observation seems to indicate that in the predominant number of instances the primary focus is most likely in some part of the respiratory or gastrointestinal tract and serves to direct the search for a suspected primary seat of the disease to these two systems.

In all of the cases in which full postmortem examination was made metastasis to the brain was found to be but an expression of a generalized process of dissemination, as other viscera were coincident sites of the metastases. The lungs, when not the primary seat of the malignant growth, were spared of recognizable metastatic lesions in only 6 cases. Of 23 cases in which autopsy was restricted to the brain, roentgen studies suggested the presence of metastases in the lungs in 7 cases. This observation also serves as a guide in distinguishing between the primary and the secondary character of an intracranial neoplasm and points to the need for a clinical investigation in almost every instance of brain tumor by every available method (gastric analysis and roentgenographic and pyelographic studies) in order to establish a probable source of metastasis.

Our material presents strong evidence that the metastatic cells are brought to the brain by the blood stream and no evidence of transportation of neoplastic cells to the brain by true lymphatics.

The growth of a metastatic tumor in the brain takes place at the expense of adjacent brain tissue. Its extension is by way of the perivascular spaces and probably also by actual transportation of small cell groups through the vascular channels.

In spite of its invasive character, a discrete line of demarcation between the metastatic tumor and the adjacent tissue is maintained, and only mild reactive changes, such as a narrow zone of condensation, gliosis and occasional lymphocytic infiltration in nearby brain tissue, are present. In rare instances a narrow belt of hemorrhage is observed, and this is particularly true of metastases from the so-called Grawitz type of tumor, or hypernephroma. Relatively wide areas of edema of surrounding brain tissue are common.

The tumor tissue itself is usually rich in blood vessels, occasionally shows extravasation but most frequently contains relatively large areas of necrobiosis. A fairly large number of such tumors contain cysts filled with gelatinous material. In a small group of cases of metastatic invasion of the brain the lesions are widespread in distribution but are restricted to infiltrations about blood vessels. These lesions are recognized only microscopically and are occasionally described as miliary carcinomas.

The choroid plexus, which was studied with a view to determining its role in the transportation of tumor cells to the nervous system, was the seat of metastatic invasion in only 1 of 57 cases.

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CORTICAL REORGANIZATION OF MOTOR FUNCTION

STUDIES ON SERIES OF MONKEYS OF VARIOUS AGES FROM INFANCY TO MATURITY

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In mammals comparable lesions of the cerebral cortex affecting motor status have far less permanent and severe effect when the injury is sustained in infancy than when it occurs in maturity.[1] This is apparent in all species in which adult motor performance is largely dominated by the cerebral cortex, as in man, monkey, dog and cat.[2] Thus, when the cortical areas 4 and 6 of Brodmann are removed from infant monkeys or chimpanzees, there is little immediate effect on motor performance and only moderate effects appear as such animals later develop.[3] In contrast, adult animals exhibit severe paresis after similar procedures (figs. 1 and 2).

The processes, anatomic or physiologic, which lie behind this striking age difference are unknown. Even the relationship of myelination to function is not certain, although much discussed. This paper deals with one obvious and immediate step in further analysis of the question, namely, the time at which the change from the reaction of the infant to that of the adult occurs. For this purpose the effects of cortical ablations on a series of 16 monkeys (Macaca mulatta) of varying ages have been compared.

METHOD

Cortical ablations were made by the technic used in this laboratory for the past ten years, with sterile precautions and with the animals under ether anesthesia. The animals were then watched for changes in posture and prehension and for weakness, paresis, spasticity or flaccidity. Tendon reflexes were examined, as well as placing and hopping responses and righting reflexes when present. The

From the Laboratory of Physiology, Yale University School of Medicine.

This study was aided by a grant from Child Neurology Research of the Friedsam Foundation.

1. Kennard, M. A.: Age and Other Factors in Motor Recovery from Precentral Lesions in Monkeys, Am. J. Physiol. **115**:138-146, 1936.

2. Kennard, M. A.: Relation of Age to Motor Impairment in Man and in Subhuman Primates, Arch. Neurol. & Psychiat. **44**:377-397 (Aug.) 1940.

3. Kennard, M. A.: Reorganization of Motor Function in the Cerebral Cortex of Monkeys Deprived of Motor and Premotor Areas in Infancy, J. Neurophysiol. **1**:477-496, 1938.

summation of all these signs and the sequence of their change were taken to indicate the stages in recovery of motor function.

The term "thalamic preparation" is used as employed first by Magnus [4] in describing decorticate animals and later by Bieber and Fulton [5] in designating monkeys after bilateral removal of areas 4 and 6 from the cortex. Such preparations, when adult, have no voluntary motor performance but exhibit tonic righting reflexes and forced grasping. Posture is characteristic (fig. 1). The monkey lies on whichever side it is placed. The undermost extremities are always extended and the uppermost always flexed. Thus the posture of the extremities is reversed when the animal is turned from one side to the other. Reflex grasping is pronounced and is always greatest in the uppermost hand and foot, which are more flexed than those lying undermost.

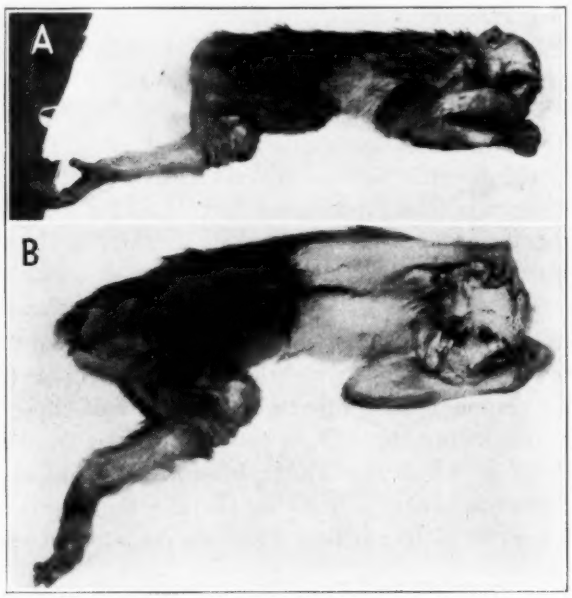

Fig. 1.—Thalamic posture of mature monkey (Macaca mulatta), (*A*) sixteen and (*B*) thirty-one days after ablation of areas 4 and 6 from both hemispheres. There has been no recovery of voluntary motor activity.

In the protocols, in which ablations of the leg, arm and face divisions of area 4 are indicated, it will be seen that in 1 experiment only was face area 4 left intact. It is probable that this influenced recovery to some degree, but the results still seem comparable to those in instances in which ablations were more radical.

The term voluntary movement is used to denote purposeful motor activity by the animal. It is opposed to stereotyped or reflex movement or grasp. Thus, the

4. Magnus, R.: Körperstellung und Labyrinthreflexe beim Affen, Arch. f. d. ges. Physiol. **193**:396-448, 1922.

5. Bieber, I., and Fulton, J. F.: Relation of the Cerebral Cortex to the Grasp Reflex and to Postural and Righting Reflexes, Arch. Neurol. & Psychiat. **39**:433-454 (March) 1938.

sight of food may stimulate one of these animals to violent involuntary movements of rhythmic alternate progression involving all four extremities—stereotyped and reflex behavior which is inappropriate for the situation, or the same stimulus may bring forth a voluntary response which may consist only of extension of the lips or of an extremity toward the food, but which, however unsuccessful in its

Results of Bilateral Ablation of Areas 4 and 6 from 16 Macaca Mulatta Monkeys of Various Ages

Experiment No.	First Operation		Second Operation		Interval Between Operations	Total Recovery During		Spasticity	Survival After Second Operation
	Age	Weight, Gm.	Age	Weight, Gm.		First Week	First Month		
1	3 wk.	400	6 mo.	850	5 mo.	Runs; climbs; feeds self	Prehension only; slightly awkward	—	2 yr.
2	3 wk. Bilateral	465	.....	.....	None	Slight postural change only	Hands used awkwardly	—	1 yr.
3	4 mo. Bilateral	850	.....	.....	None	Rights; stands; progression poor	Climbs; clings; runs poorly	—	1 mo.
4	3 mo.	925	6 mo.	1,200	3 mo.	Walks; climbs; prehension poor	Runs; slightly awkward; feeds with hands	—	2 yr.
5	4 mo.	1,100	6 mo.	1,250	2 mo.	Thalamic posture first day; later rights and stands	Balance poor; no prehension; feeds self; progression poor	+	2 yr.
6	..... Bilateral	1,400	.....	.....	None	Rights and stands	Cannot feed self (16 days)	+	16 days
7	.....	1,750	.....	1,600	2 mo.	Thalamic posture	.....	+	10 days
8	..... Bilateral	1,800	.....	.....	None	Rights; stands occasionally; cannot feed self	No change (19 days)	++	19 days
9	.....	1,860	.....	2,300	8 mo.	Thalamic posture; rights	Stands; walks; cannot feed self	++	
10	.....	2,100	.....	2,300	4 mo.	Thalamic posture; no righting	.....	+	10 days
11	..... Bilateral	2,900	.....	.....	None	Thalamic posture	No change	+++	24 days
12	.....	3,000	.....	2,900	10 wk.	Thalamic posture; rights from right side	No change	+++	40 days
13	.....	3,300	.....	3,100	2 mo.	Thalamic posture; rhythmic struggling	Rights from right side	+++	12 days
14	.....	3,700	.....	3,200	6 wk.	Thalamic posture	No change (21 days)	+++	21 days
15	.....	4,200	.....	4,200	3 mo.	Thalamic posture; no righting	No change	+++	48 days
16	.....	8,700	.....	8,700	4 days	Thalamic posture	No recovery	++++	8 days

accomplishment, is to some degree an appropriate response for the subject under the given circumstances.

In the macaque a rough correlation of ages and weights is as follows: birth, 300 to 500 Gm.; 6 months, 1,250 to 1,500 Gm.; 1 year, 2,000 to 2,300 Gm.; maturity, during the fourth year of life, 4,500 to 6,000 Gm. for females and 5,000 to 8,000 Gm. for males. The exact ages of the animals in this series born in the colony are given in the table; for the others, age must be estimated roughly from weight.

PREVIOUS OBSERVATIONS

Earlier experiments on a larger number of adult and infant monkeys (chimpanzees, baboons and cebus monkeys, as well as macaques) had disclosed several facts by which the course and extent of recovery in an animal following a specific lesion could be accurately predicted. In these experiments ablations were made from areas 4 and 6 and also from many other portions of the sensorimotor cortex. The results were consistent in all instances. All operations were performed on the infants during either the fourth week or the sixth month of life. The results for the group may be summarized as follows [6]:

1. In infants, during the first month of life, unilateral or bilateral ablations from the sensorimotor cortex have little effect on immediate motor performance, and the late effects of such early operations are also minimal as compared with those of removal of similar areas from adult monkeys.

2. The size of the lesion is of more consequence in the infant than in the adult. In either instance a lesion comprising the arm division only of area 4 produces less motor deficit in the arm than does a larger lesion involving the arm, leg and face divisions.

3. In the case of bilateral extirpations from the sensorimotor cortex, simultaneous ablations produce greater deficit than do seriatim ablations. The total ultimate deficit is inversely proportional to the length of time and the degree of recovery which has taken place between operations.

These findings thus emphasized for the infant what had already been firmly established for the adult, namely, that there is bilaterality of function in the cortex of the monkey and chimpanzee and that within one hemisphere removal of a functional unit results in some degree of reorganization of the remaining cortex and consequently in recovery of function.

PRESENT OBSERVATIONS

The data from 16 macaques have here been assembled. Each animal was of a different age, either known or estimated from the weight of larger animals. In each animal areas 4 and 6 only were extirpated. In the table the animals are listed in order of body weight at the first operation and their motor status during the first week and at the end of the first month after bilateral ablation is recorded. Abstracts of the protocols of 5 of these animals which were selected as representative of the various ages from infancy to maturity follow. Each illustrates the course of the recovery of motor function at a particular age.

6. Kennard (footnotes 2 and 3).

PROTOCOLS

EXPERIMENT 1.—*Seriatim ablation of areas 4 and 6 (leg and arm) at 3 weeks and 6 months of age. Immediate recovery of walking, climbing and feeding, with use of hands. Final deficit in fine prehension only.*

Nov. 27, 1933.—Born; weight 365 Gm.

December 18.—Age 21 days; weight 400 Gm. Motor performance at this time was largely confined to clinging and sucking. Reflex grasping was pronounced. The righting reflexes were present. The animal could crawl slowly and on a wide base.

First Operation: Extirpation of areas 4 and 6 (leg and arm) on the left side.

Postoperative Notes.—First day: Motor performance was unchanged except that the right extremities were slightly more extended than the left and the grasp on the right side fatigued easily. There was no increase in resistance to passive manipulation.

Ninth Day: Postural differences between the two sides had disappeared. Motor performance was entirely normal for an infant of this age.

Sixth Month of Life: Posture was normal, and all movements, including fine voluntary prehension, were equally well executed on the two sides. There was, however, a tendency to use the left hand in preference to the right for fine prehension whenever choice was possible.

May 28, 1934.—Age 6 months; weight 850 Gm.

Second Operation: Extirpation of areas 4 and 6 on the right side.

Postoperative Notes.—First Day: Forced grasping reappeared in both hands with voluntary movement also in the right hand. Movements on the right were of normal intensity and pattern, but on the left there was little spontaneous movement. Righting, standing and walking were adequately, but somewhat slowly, performed. Climbing was quicker and more accurate.

Twentieth Day: The animal appeared slightly awkward but ran, climbed and walked well. The extremities on the left were held slightly extended, and coordination was poorer on this side. Resistance to passive manipulation was slightly increased on the left side, and the left hand was not used in feeding if the right was available.

Third Month: The infant had now become very agile, running, climbing and jumping only slightly more slowly than is normal at that age. Small objects were well picked up, and the "grooming," or fleapicking, act was performed with discrete finger movements, but the accuracy and force of the fingers were noticeably not as well regulated as in normal animals. There was no spasticity. During the subsequent two years there was no further improvement.

EXPERIMENT 2.—*Simultaneous ablation of areas 4 and 6 (leg, arm and face) at the age of 22 days. Inconspicuous effect on motor performance. Final deficit in prehension and speed of movement. No spasticity* (fig. 2).

Jan. 8, 1940.—Born; weight 462 Gm.

January 30.—Age 22 days; weight 465 Gm. Motor performance was normal. The infant could right itself and crawl slowly on a broad base. It clung by preference. Reflex grasping and sucking were well developed. There was no voluntary prehension.

First Operation: Bilateral ablation of areas 4 and 6.

Postoperative Notes.—First Day: The infant was able to right and showed spontaneous rhythmic crawling movements, as before operation, but fatigued easily. Reflex grasping was extreme. In sucking the bottle it also assumed postures similar to those seen before operation. Resistance to passive manipulation was diminished. Facial expression was rather set, but it blinked, sucked and vocalized appropriately.

Seventh Day: The infant had become more active and was able to climb out of its box. Moreover, in both climbing and clinging the postures were like those assumed before operation. But walking was on a broader base, with clawlike spreading of the fingers and toes. The digits were not used well for balancing or progression.

Seventeenth Day: Walking had increased in speed and improved in coordination, but the posture was unchanged. Motor development at this stage was definitely retarded as compared with that of a normal infant of the same age.

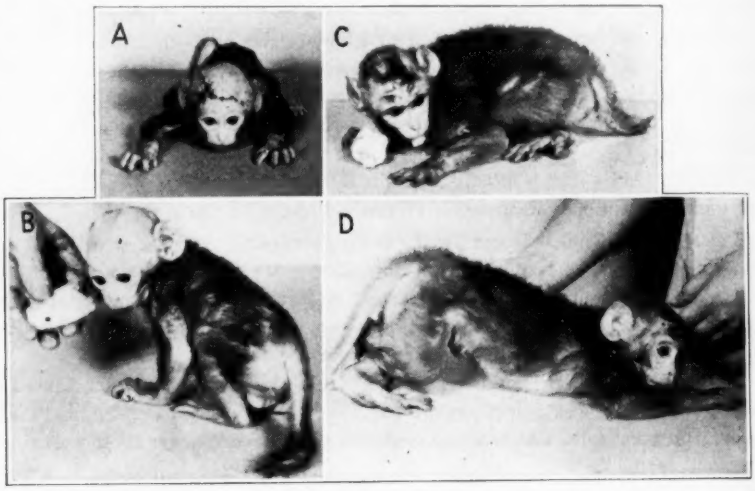

Fig. 2.—Recovery of motor activity in a 3 week old monkey (Macaca mulatta) after simultaneous bilateral ablation of areas 4 and 6. *A* and *B* were taken on the third postoperative day; *C* and *D*, eleven months later.

Thirty-Fifth Day: The infant walked rapidly and ran slowly. When approaching food on the floor, it brought its lips in contact with the food without using its hands. There were no discrete finger movements. Resistance to passive manipulation was not increased.

Sixth Month of Life: Total motor performance was not much more complex than on the thirty-fifth postoperative day. The hands were poorly used for feeding. A "scissors" gait had developed in the hind extremities, with pronounced adduction of the thighs and flaring of the fingers and toes (fig. 2). Resistance to passive manipulation was moderately increased.

Twentieth Month of Life (present age): There has been no change in motor status. The postural deformity is increased by the contractures, and the resistance to passive manipulation is definitely greater than that of normal animals.

EXPERIMENT 4.—*Seriatim ablation of areas 4 and 6 (leg, arm and face) at ages 3 and 6 months. Immediate loss of fine movements; increased slowness and awkwardness in progression; return of reflex grasp. Final deficit: moderate spasticity, awkwardness in progression and poor prehension* (fig. 3).

April 23, 1939.—Born; weight 500 Gm.

August 2, 1939.—Age 3 months; weight 925 Gm.

First Operation: Extirpation of areas 4 and 6 on the left side.

Postoperative Notes.—First Day: The animal used all four extremities for walking and climbing. The right arm and leg were held more extended than the left, and the fingers and toes of the right limbs did not move discretely for prehension. Resistance to passive manipulation was diminished on the right side, and knee jerks were absent. There was no facial weakness.

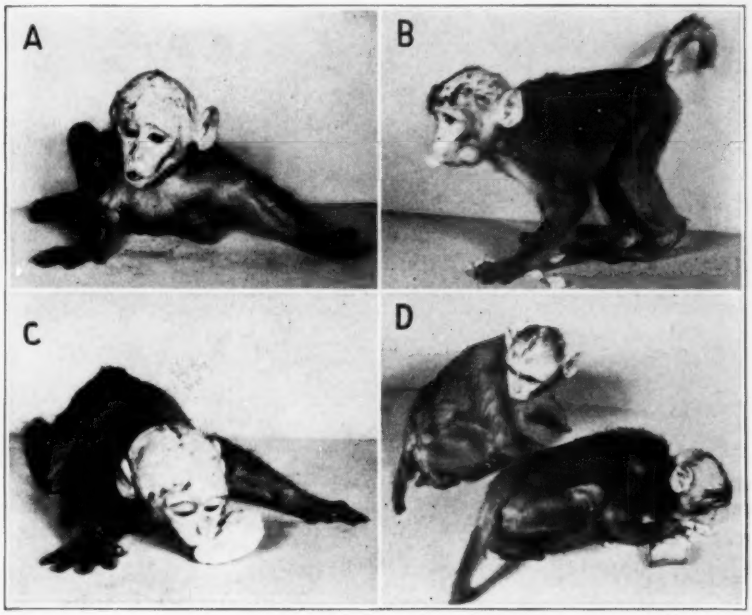

Fig. 3.—Recovery of young monkey (Macaca mulatta) after bilateral seriatim ablations of areas 4 and 6 during the third and the sixth month of life, respectively. *A* and *B* were taken on the second postoperative day, when the monkey righted and fed itself; *C* and *D*, three months later (see figure 4).

Twenty-First Day: There was a slight postural difference between the two sides, and the left hand was used in preference to the right. No other deficit was noted. The condition remained unchanged until the second operation.

Oct. 23, 1939.—Age 6 months; weight 1,200 Gm. Extirpation of areas 4 and 6 on the right side.

Postoperative Notes.—First Day: The animal lay on its side but could right easily and made incoordinated efforts at rhythmic progression. It was able to drink and eat when food was held to its mouth. There was slight weakness of the left side of the face.

Second Day: The animal stood and walked poorly, reaching for food with the right hand only. Reflex grasping had reappeared bilaterally.

Fourth Day: The animal could climb and walk rapidly, but on a wide base. It pushed food toward its mouth with its hands and at times grasped it awkwardly.

Eighth Day: The animal was now able to walk well but ran slowly. When eating, the food was supported with the hands, but there were no fine prehension movements. No spasticity was evident.

Twentieth Day: There was some improvement in speed and coordination, but the use of the fingers remained poor. The knee jerks were moderately hyperactive, but resistance to passive manipulation was not increased. The tendency to climb and cling persisted, although there was no true reflex grasping.

Sixtieth Day: Not much change was evident. The animal still walked on a broad base, with slight exaggeration of the movements. The hands were everted and the legs slightly "scissored." Resistance to passive manipulation had become slightly increased.

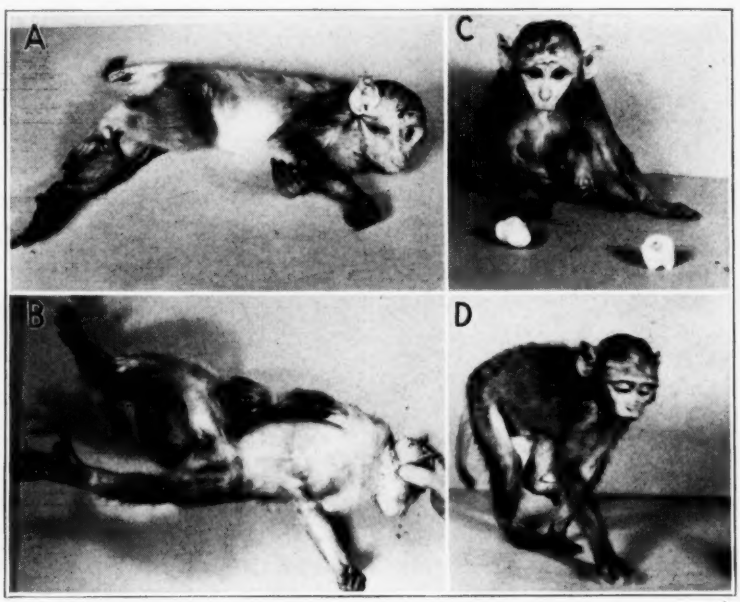

Fig. 4.—Recovery of a young monkey (Macaca mulatta) after bilateral seriatim ablations of areas 4 and 6 at four and six months of age, respectively. *A* and *B* were taken on the second postoperative day, when voluntary motor power was absent and righting reflexes were present; *C* and *D*, ten months later. Compare with figure 3, photographs of an infant monkey which was operated on one month earlier and showed greater recovery.

EXPERIMENT 5.—*Seriatim ablation of areas 4 and 6 (leg, arm, face) at 4 and 6 months of age. Immediate loss of all voluntary power. Thalamic posture only for three days. Gradual recovery of righting and standing. Animal ultimately walked, climbed and fed self* (fig. 4).

April 27, 1939.—Born; weight 510 Gm.

September 6.—Age 4 months; weight 1,200 Gm.

First Operation: Extirpation of areas 4 and 6 on the left side.

Postoperative Notes.—First Day: Although the animal was able to walk about the cage, the right extremities were extended and dragged slightly. Reflex grasping had returned to the right hand, and spontaneous movements were more frequent on the left side than on the right.

Fiftieth Day: The posture had become symmetric except that during fatigue the right extremities dragged slightly. The fingers of the right hand were not used discretely in feeding.

October 30.—Age 6 months; weight 1,250 Gm.

Second Operation: Ablation of areas 4 and 6 on the right side.

Postoperative Notes.—First Day: The animal remained lying on whichever side it was placed, and there was no righting. Reflex grasping was bilateral and of moderate intensity. Resistance to passive manipulation was not increased.

Third Day: The animal could now right itself from either side and occasionally stand, although it usually fell over. There was no voluntary prehension. Tube feeding was necessary.

Fourth Day: The animal could now walk and eat by crouching over food and approximating the mouth to it without the use of its hands. It could also move the right hand in a desired direction but was unable to grasp voluntarily. Resistance to passive manipulation was slightly increased.

Thirteenth Day: The hands were used for shoving food into the mouth, but reflex grasping persisted. The extremities were held extended so that the animal walked as though on stilts. Resistance to passive manipulation was increased, and the knee jerks were extremely active. Flicking of one finger or toe produced reflex flexion of all other digits of a given extremity.

Forty-Third Day: The performance could not now be distinguished from that of the monkey in experiment 3, its cage mate and of the same age, which had been operated on when younger. Progression was on a broad base, and the fingers were awkwardly used. There was no subsequent improvement.

EXPERIMENT 9.—*Seriatim ablation of areas 4 and 6 (leg, arm and face) at about 10 and 18 months of age. Loss of voluntary motor power and maintenance of thalamic posture for about one week. Gradual recovery of standing and walking postures. Reflex grasping pronounced. Stereotypy and limited pattern of movement. Animal unable to feed self.*

Feb. 25, 1941.—Age estimated at 10 months; weight 1,800 Gm. Motor performance was fully developed and was as skilled as that of an adult.

First Operation: Ablation of areas 4 and 6 on the left side.

Postoperative Notes.—First Day: The animal was able to climb, but the fingers and toes on the right side were used poorly. There was slight weakness of the right side of the face.

Sixth Day: Reflex grasping was moderate in the right hand and slight in the right foot. The right side fatigued easily in climbing and jumping. Fine finger movements were absent on the right side.

Eighth Month: The deficit on the right side was minimal, but the animal preferred to use the left hand for fine movements.

October 30.—Age about 18 months; weight 2,700 Gm.

Second Operation: Ablation of areas 4 and 6 on the right side.

Postoperative Notes.—First Day: The animal lay in the thalamic posture on whichever side it was placed. There was no righting, but tonic righting neck reflexes were present. Reflex grasping was extreme bilaterally. Resistance to passive manipulation had become moderately increased and was always greatest in the undermost extremities.

Third Day: The animal could now right itself from the right side onto the belly but could neither stand nor maintain balance. Automatic progression movements were violent and stereotyped. Spastic muscles of the jaw necessitated tube feeding.

Ninth Day: The animal had made no attempt to climb out of its box but righted itself easily from either side and sat motionless on the floor until disturbed. It could then stand, walk and run rapidly but extremely unsteadily. Motions were automatic and continued until stopped. It bit at food in the same manner but did not swallow food taken into the mouth. There was no attempt at voluntary prehension.

Fifteenth Day: The monkey was now able to walk, climb and feed itself inaccurately by bringing the face to the food on the floor. There was greatly increased resistance to passive manipulation. Progression was awkward because of the spasticity, and falling was frequent. The hands were still not used for voluntary prehension.

EXPERIMENT 15.—*Seriatim ablation of areas 4 and 6 during the third year of life. Thalamic posture, reflex grasping and severe spasticity after last operation. Status maintained for forty-eight days, without recovery* (fig. 1).

Nov. 26, 1932.—Age about 3 years; weight 4,200 Gm.

First Operation: Extirpation of area 6 on the left side.

Jan. 4, 1933.—Second Operation: Extirpation of right area 6.

January 27.—Third Operation: Extirpation of left area 4.

February 1.—Fourth Operation: Extirpation of right area 4.

Postoperative Notes.—First Day: The animal lay as placed, assuming the thalamic posture without any righting. There were paroxysmal struggling movements when it was disturbed. Reflex grasping was pronounced and resistance to passive manipulation greatly increased.

Fifth Day: There was no change. Perseveration of chewing movements appeared, but swallowing of solids remained impossible.

Tenth Day: The animal still could not right itself, and the thalamic posture was unchanged. But when food was placed in the field of vision a movement toward it was executed by the right arm.

Fifteenth Day: The animal occasionally righted itself with spontaneous rhythmic movements as its strength improved; otherwise there was no change.

Twenty-Fifth Day: The animal continued to be unable to right itself or to stand. Reflex grasping was pronounced. The thalamic posture was becoming modified by flexor contractures in the elbows and wrists and by adduction and extension in the hips and knees.

Forty-Eighth Day: No further change in motor status had appeared. Spasticity continued to be extreme, and movement was more limited by the contractures.

COMMENT

A capacity of the central nervous system for reorganization which enables its remaining portions to integrate motor performance when areas 4 and 6 have been eliminated is here found to be directly related to age. Furthermore, at least during the first two years of a monkey's life, or half the distance to maturity, the changes in the capacity for reorganization are gradual.

It can be seen in the table that every animal weighing less than 2,300 Gm. recovered some degree of voluntary motor power but that those above this weight never showed such recovery. That the change is gradual is well demonstrated by these 16 animals, for the first 5, all less than 6 months old, were able to feed themselves, as well as walk, run and climb, after bilateral ablations. The older of these 5 monkeys, however, had not the skilled prehension acquired by monkeys 1, 2 and 3, which were operated on during the first months of life.

Monkeys 6 to 10 all recovered some degree of voluntary power, but in no instance sufficient for adequate feeding or cage activity during the first postoperative month. However, this group of animals, aged approximately 1 year, showed greater capacity for functional reorganization than did monkeys 11 to 16, all of which were 2 years old.

Although the change from the reactions of the infant to those of the adult came gradually, it was in the second group, animals 6 to 10, that the greatest loss of ability to reorganize took place. Experiments 4 and 5 (table and protocols) demonstrate this particularly clearly. Monkey 4, operated on at 3 and 6 months of age, respectively, was able to stand, walk and feed immediately after operation (fig. 3). Monkey 5 (born one day before monkey 4), which was operated on at 4 and 6 months of age, respectively, had so much more deficit that for forty-eight hours after the second operation the animal showed only thalamic involuntary patterned movement and the tonic righting reflexes (fig. 4). Yet by the end of the month this animal could in no item of motor performance be distinguished from monkey 4, its cage mate (fig. 2 *D*).

Experiment 9 illustrates the reactions of a slightly older animal (see protocol). At the ages of 10 and 18 months this monkey was subjected to extirpation of areas 4 and 6 on the left and the right side, respectively. Recovery was sufficient so that at the end of a month the animal could stand and walk, although for the first postoperative week it had been barely able to right itself. It could bring its face in contact with food placed on the floor and could bite, but the effort was poorly directed and executed and supplementary feeding by tube was necessary to maintain adequate nutritional state. Beyond this age there was little evidence of recovery.

That reorganization is greater when ablations from the two hemispheres are performed seriatim is well demonstrated in this series. Experiments 1 and 2 were both carried out on young infants; yet the recovery in the case of monkey 1 was greater than in that of monkey 2 because there was an interval of five months between operations in the first case. In the higher age groups, the same can be shown in experiments 8 and 9, both animals being of about the same weight. Recovery

was greater in the case of monkey 9 than in that of monkey 8 because the former had an interval of eight months between operations and the latter none.

The relation of spasticity to recovery or reorganization seems also to be definite, although the significance of this is by no means certain. All the young animals which showed notable recovery of voluntary motor coordination had little or no immediate spasticity, whereas spasticity increased with age at operation in the animals operated on after the first year. It has been previously shown that ablations made on animals during the first month of life produced no immediate spasticity and that although it later develops in these monkeys during the second six months of life, it never becomes as severe as when operations are performed at a later age.

This process of reorganization has definite characteristics, as shown in the protocols here given and in the records of many other monkeys with either unilateral or bilateral lesions of the sensorimotor cortex, varying in extent from one entire hemisphere to small discrete lesions of a part of one gyrus.

That reorganization takes place within the remaining portions of the cortex has been shown previously,[3] since removal of such regions as the prefrontal area or the postcentral gyrus greatly augments motor deficit when areas 4 and 6 have been previously extirpated in infancy, whereas ablation of the prefrontal or the postcentral area from a normal cortex has no effect on skilled motor acts.

It has been shown, also, that the process of reorganization is a slow one, requiring many months for maximal recovery both in the infant and in the adult. The order of recovery of function is, of course, predictable, function returning first in the more proximal muscle groups and last to finer movements of the digits.

Finally, this ability to reorganize is slowly lost during almost the entire growth period of the young animal and does not rapidly disappear during the first months, as originally surmised.[7]

In normal animals there are histologic structures from both the prefrontal and the postcentral cortex which may permit reorganization. These are the Betz cells in the postcentral gyrus and direct connections from areas 9 to 12 of the frontal lobe to subcortical motor centers.

If the reorganization is entirely functional then the reflex arcs established via these normal pathways must be sufficient to integrate motor activity. Understanding of the process is little helped by utilization of the biologic fact that the young cell is always more capable of adapting than is the old. Nor are there as yet any simple known physical, chemical

7. Kennard (footnotes 1 and 2).

or anatomic processes to explain the fact that learning of any type, particularly that which is cortically integrated and complex, is always far more easily and competently accomplished by the young.

If the process of reorganization is anatomic there are several possibilities, none of which can be satisfactorily proved at the moment, since the cytologic development of the monkey cortex is not known.

If myelination and function are to be correlated, which is by no means certain, then reorganization must be greater before complete myelination takes place. It is not known when this occurs in the monkey, but evidence indicates that it is well before the end of the second year of life. A more satisfactory anatomic explanation, which would account for all the changes if it were true, would be that of the growth of dendrites. During fetal life and immediately after birth the dendrites in the human cortex proliferate and ramify.[8] The motor cells in the infant monkey show no differentiated Nissl bodies during at least the first three months after birth. Development of the neuron and proliferation of the dendrite must therefore take considerable postnatal time. If, during this stage, the neurons with which the proliferating dendrites would normally form synapses were removed, it is easy to imagine that other synapses would be formed in less usual combinations and the result might be the integration of reflex arcs through unusual parts of the cortex. Some adaptation of the theory of neurobiotaxis [9] might be made to fit the process of organization of a new functional and anatomic pattern of reorganization.

The extreme slowness of the procedure would fit well with this idea of actual growth of the neural process. It could explain also the fact that in either the infant or the adult, but to greater extent in the infant, recovery of function is more complete when extirpations are made seriatim and that small lesions have less effect on motor performance normally integrated through the extirpated area than have lesions which include adjacent areas as well.

Present knowledge is insufficient for more than the foregoing suggestions concerning the process behind cortical reorganization. But whether it is physiologic, and related to learning, or anatomic, and related to growth of dendrites, or both, it is probable that the factors which facilitate cortical organization in the normal young are the same by which reorganization is accomplished in the imperfect cortex after injury.

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8. Conel, J. L.: The Cortex of the Newborn, in The Postnatal Development of the Human Cerebral Cortex, Cambridge, Mass., Harvard University Press, 1939, vol. 1.

9. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: Comparative Anatomy of the Nervous System of Vertebrates Including Man, New York, The Macmillan Company, 1936.

CONCLUSIONS

1. The cerebral cortex of the young monkey, Macaca mulatta, possesses greater capacity for reorganization than does that of the mature animal, as shown by recovery of motor function following bilateral ablation of areas 4 and 6.

2. The greatest reorganization occurs during the first six months of life.

3. The greatest loss of capacity to reorganize occurs during the end of the first year of life, at the same time that spasticity begins to appear.

4. The recovery, previously shown to be due to reorganization of function in the remaining areas of the cortex, is slow and is maximal when ablations are carried out seriatim and with long intervals between extirpations.

5. It is suggested that this is compatible with the anatomic structure and growth of the cortex and that the dendritic connections of the motor neurons already present in the unexcised areas are reorganized during the period of recovery of function.

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PATHOLOGY OF SENILE BRAINS

I. SILVER-REDUCING STRUCTURES IN THE HIPPOCAMPUS

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Although the hippocampus has long been a favorable site for the study of senile changes in the brain,[1] this region has never been fully explored. The present communication is devoted to observations of a qualitative nature, made with the use of a method hitherto not employed for this purpose,[2] on the hippocampal formation in senile brains.

In the investigation of senile changes in the brain, the silver impregnations have furnished the principal histologic technic. The Bielschowsky method, or one of its modifications, designed for the exhibition of axis-cylinders and endoneurofibrils, has been chiefly employed. The latter structures, as shown in a previous paper,[2] are the least argyrophilic in the nervous system and frequently require most meticulous technic for their demonstration. On the other hand, the senile plaques and Alzheimer strands are strongly argyrophilic. It is of interest that these pathologic structures are partly masked when very careful neurofibrillar technic is followed. As long ago as 1910 Fischer [3] pointed out that certain types of plaques are best seen when the Bielschowsky method fails to impregnate the axis-cylinders, that is, when the method is unsuccessful in the purpose for which it was originally designed. Alzheimer [4] observed the

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1. (*a*) Simchowicz, T.: Histologische Studien über die senile Demenz, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1911, vol. 4, pp. 267-444. (*b*) Spielmeyer, W.: Histopathologie des Nervensystem, Berlin, Julius Springer, 1922. (*c*) Grunthal, E.: Klinisch-anatomisch vergleichende Untersuchungen über den Greisblödsinn, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:763-818, 1927.

2. King, L. S.: The Impregnation of Neurofibrils, Yale J. Biol. & Med. **14**:59-68, 1941.

3. Fischer, O.: Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung, Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:371-471, 1910.

4. Alzheimer, A.: Ueber eigenartige Krankheitsfälle des späteren Alters, Ztschr. f. d. ges. Neurol. u. Psychiat. **4**:356-385, 1911.

same thing in 1911. And more recently, using the same method, Alexander and Looney [5] commented that fibrillary change may be better demonstrated in faulty than in successful impregnations.

Some of the reasons for these difficulties were discussed previously,[2] when the relative argyrophilia of different constituents of the nervous system was considered. The use of silver nitrate, ammoniacal silver and a reducing agent, as in the Bielschowsky or the Hortega technic, is a complicated procedure, giving brilliant results in the demonstration of endofibrils and axis-cylinders when completely successful. Under such conditions, however, the sensitizing preliminary bath of silver nitrate sometimes diminishes the staining properties of senile plaques and Alzheimer strands. And, unfortunately, for reasons not as yet clear, fully successful impregnations are all too often not obtained, or are even unobtainable. Confusing artefacts may be produced which bear a striking resemblance to "pathologic" changes described in the literature. Moreover, many nerve cells may exhibit, instead of endofibrils, granular or lumpy masses of silver-staining material the nature of which has never been established and which are very difficult of interpretation, especially in diseases such as senile dementia, in which endocellular argyrophilic masses are of prime significance.

In a previous paper a new technic, or rather a new application of an old technic, was therefore advocated, using a quite different principle. Instead of employing a sensitizing and a reducing bath in conjunction with the ammoniacal silver, the latter alone, in the form of silver carbonate, is used. The reducing power inherent in the tissue constituents is utilized, facilitated by gentle heat. Under these conditions, all nuclei stain normally, together with the bare outline of the perikaryon, and rarely a few axis-cylinders. The mass of axis-cylinders and the endofibrils are left unstained. However, senile plaques, Alzheimer strands and variously altered tissue constituents possess high reducing power for the ammoniacal silver and stand out vividly. Artefacts produced by reducing substances in the solution of formaldehyde are eliminated. There is no suppression by preliminary treatment, no obscuring of the abnormal by the normal, no difficulties due to "faulty" impregnation and no confusion of interpretation. Detailed steps of this method are found in a previous paper.[2]

CELL CHANGES

The type of fibrillary change that predominates in the neocortex is well known.[2] In the hippocampus, however, the characteristic cell change

5. Alexander, L., and Looney, J. M.: Histologic Changes in Senile Dementia and Related Conditions Studied by Silver Impregnation and Microincineration, Arch. Neurol. & Psychiat. **40**:1075-1110 (Dec.) 1938.

is that appearing in figure 3 *A*, in which the cells are pear shaped and filled with more or less parallel fibrils, relatively straight and usually fine and delicate. The apical and basal dendrites are not involved. These may with propriety be called pyriform Alzheimer cells.

These pyriform cells exhibit an extensive series of gradations of a disintegrative character. The delicate, relatively straight fibrils are

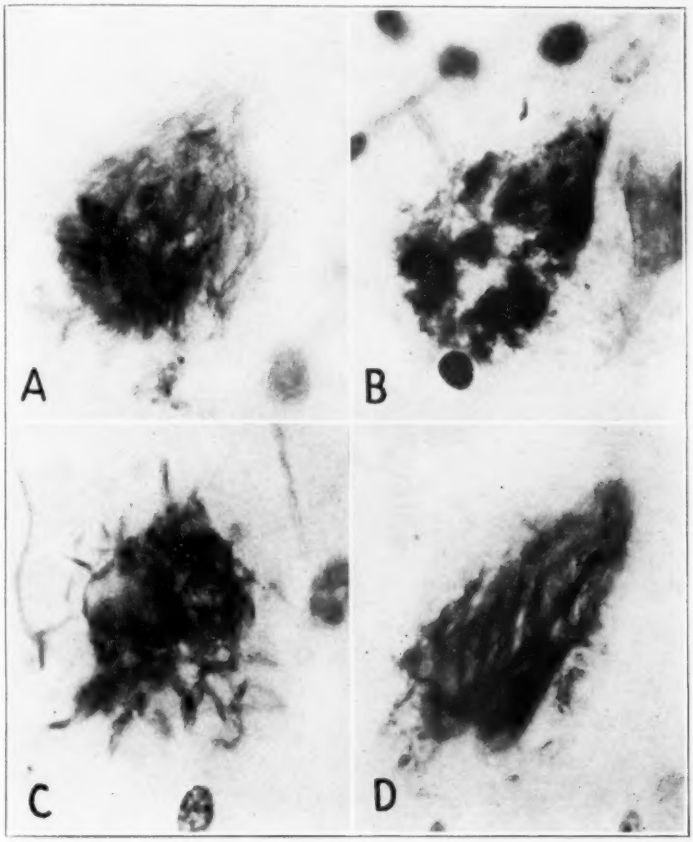

Fig. 1.—Cells of the pyriform type, exhibiting pronounced Alzheimer change. × 1,200. In *A* the fibrils are very delicate and tend to fray out beyond the confines of the cell into the interstitial tissue. In *B* the argyrophilic material is broken up into coarse, lumpy, conglomerated masses of fibrils, evidently a disintegrative process. In *C* the cell has an irregular outline, with radially arranged fibrils. This cell suggests an early plaque. In *D* the fibrillar change within the pyriform cell is well marked. Around the periphery, especially on the right side, there are many short perpendicularly oriented threads in the interstitial tissue which suggest plaque material.

frayed or condensed; they become awry and convoluted, instead of parallel, and may break up into small masses and groups. Figure 1

illustrates certain of these changes, which are considered to be later stages than the regular cell forms shown under lower magnification.

In preparations stained by the recommended method, many of these pyriform cells show most intimate relations to certain accretions of argyrophilic material. In the center of figure 3 *A* one cell is surrounded by small clublike masses, closely applied to the surface of the cell, but not continuous with the fibrillar material within the cell. These small

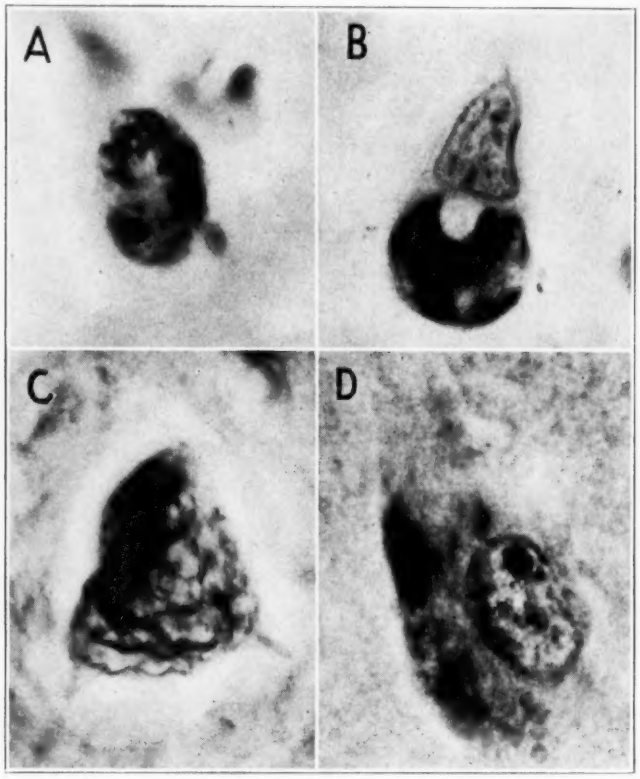

Fig. 2.—Various cell changes in the pyramidal band of the hippocampus that are not of the pyriform type. In *A* the peripheral portions of the cytoplasm are occupied by short thick threads in disorderly arrangement, giving what may be called a "random, pen scratches" effect. × 1,000. *B* illustrates a tight, nonfibrillar argyrophilic ball in the basal portion of the cell. × 1,200. In *C* the cytoplasm is occupied by a fenestrated membrane forming definite interstices. × 1,200. The pyramidal cell in *D* shows the type of change that is much more common in the neocortex. At the margin are heavy strands of a clearly fibrillar nature, which, however, are discontinuous. A few other short strands are situated above the nucleus. × 1,200.

clubs frequently have delicate filamentous prolongations and suggest huge hypertrophied *boutons terminaux* that have become intensely argyro-

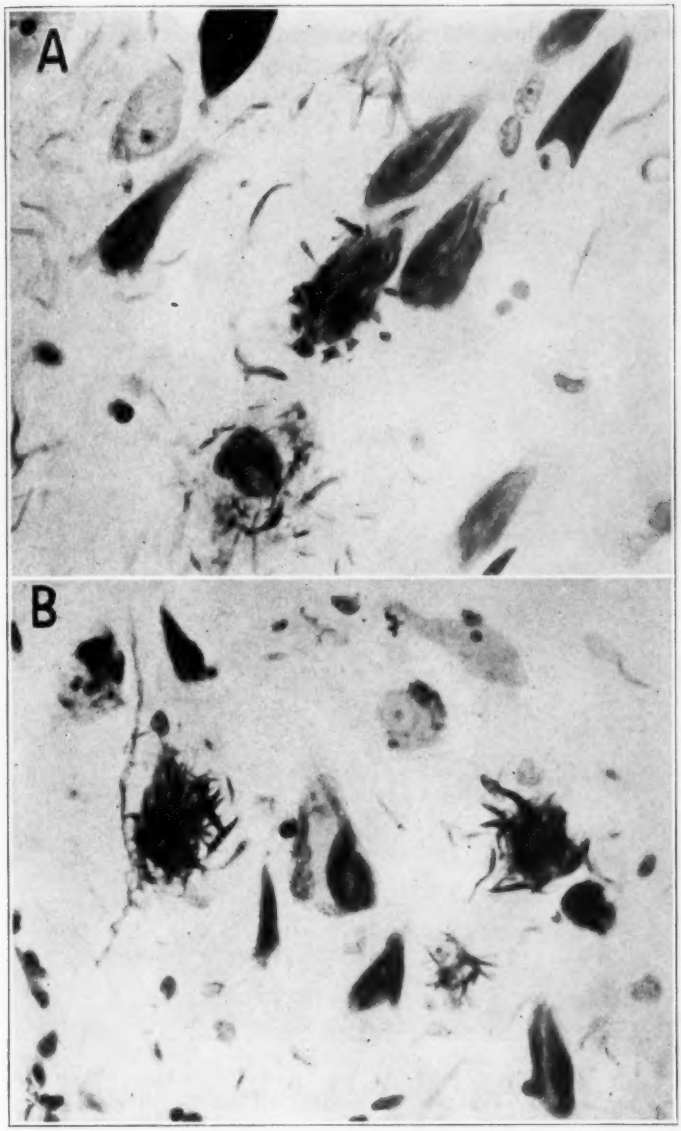

Fig. 3.—Photographs of lower magnification of the loose pyramidal cell band of the hippocampus, illustrating predominantly the pyriform type of change. In *A*, in the center of the field, a cell shows at its periphery numerous clublike endings that suggest hypertrophied *boutons terminaux*. In the lower portion of the field a cell is in intimate relation with plaque material. × 660. *B* shows two cells, at the left and the right of the center, which are affected with the Alzheimer change and, in addition, are closely surrounded by pericellular plexuses of fibers that are strong silver reducers. The normal axis-cylinders are not stained by this method. In the upper central portion of the figure is a faintly stained cell showing "pen scratch" changes. × 600.

philic. In figure 3 *A* are two pyriform cells intimately surrounded by clusters of short, plump fibrils, again quite unconnected with the interior of the cell. These clusters are slightly reminiscent of basket fibers

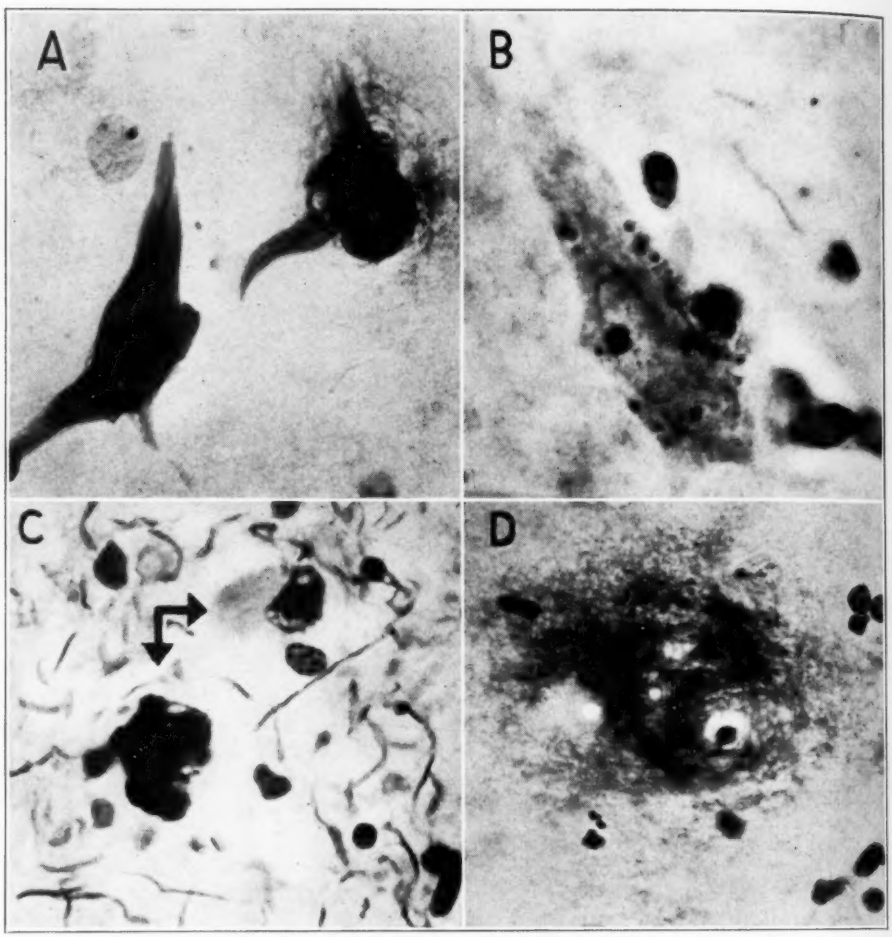

Fig. 4.—*A*, hippocampal cells affected by the Alzheimer change which is notably fibrillar but in which the cell outlines are excellently preserved and the Alzheimer material entirely contained. These cells are in a quite different category from the alterations illustrated in figure 1. The cell to the right is surrounded by plaque material that has no connection with the Alzheimer strands. × 900. *B*, an instance of granulovacuolar degeneration, the same method of impregnation being used throughout. × 1,350. In *C* the arrows point to two cells affected by a still different type of the Alzheimer change. The cell to the right has faintly outlined cytoplasm, within which is a gnarled, pretzel-like arrangement of silver-reducing material. The lower arrow points to a relatively huge, knotted and convoluted mass which appears to be a larger edition of the same type of change. No cell body is distinguishable in the latter formation. × 800. In *D* is a fine-fibered plaque, the type that is most common in the hippocampus. × 580.

surrounding Purkinje cells in the cerebellum and suggest pericellular plexuses of nerve fibrils that have also become strongly argyrophilic. Some of these fibrils may perhaps be of glial nature.

A still different alteration is shown in figure 1 *D*, in which a single pyriform cell, seen under oil, shows a faint corona of extremely fine, threadlike particles, mostly oriented in a direction perpendicular to the surface of the cell. In the illustration only those threads at the right and bottom of the cell are in focus. These short threads do not resemble *boutons* or nerve or glial fibrils. They call to mind two possibilities: (*a*) very early formation of a threadlike plaque, immediately surrounding an Alzheimer cell, a process of which figure 4 *A* (right) illustrates a much later stage, and (*b*) fraying out of Alzheimer strands beyond the cell confines into the interstitial tissue. In favor of this is the suggestive continuity between the Alzheimer strands and the surrounding threads. These two possible interpretations are by no means mutually exclusive, and, as will be shown in the section entitled "Comment," both may be correct.

Thus, many cells which exhibit pronounced Alzheimer changes are in close contact with argyrophilic material of diverse types. That is, the argyrophilia affects not only the interior of the cell but the interstitial tissue forming the immediate cell environment. The nature of this material, both within and surrounding the cell, will be discussed later.

The typical pyriform cell is characterized by involvement of the entire cell body at one time, with, for the most part, sparing of the apical and basal dendritic processes. Other types, at least initially, show a silver-reducing substance in patchy formation throughout the cell.

Marginal strands of argyrophilic material are shown in figure 2 *D*. This type of change is not uncommon in the neocortex. In figure 5 *A* a large pyramidal cell shows very heavy silver masses high in the apical dendrite as well as in the supranuclear region, together with discontinuous strands coursing through the cell. Figure 5 *B* illustrates a supranuclear tangle of argyrophilic material which breaks up in the upper portion of the cell and becomes united again high in the apical dendrite. The dark circle in the lower part of the cell represents the nucleolus, with a nuclear membrane somewhat out of focus.

These three cells are examples of a process in which the pathologic change appears intimately related to the preexisting endofibrils, representing either the original fibrils themselves or a coating or deposition of some endogenous substance on the fibrillar framework.

On the other hand, similar argyrophilic material in cells may have no conceivable relation to endofibrils. It is well known that when lipoid accumulates in nerve cells the endofibrils are pushed to one side and the lipoid droplets are enclosed within a plasmatic framework entirely free

of neurofibrils. Bielschowsky [6] in 1911 first described pathologic argyrophilic material in this plasmatic framework, but his observation received surprisingly little attention. In the present study numerous examples of this change are observed. The cells in question are crammed with lipoid droplets, embedded in a cytoplasmic meshwork much of which is capable of reducing ammoniacal silver. In figure 6 are illustrated two such cells. The argyrophilic material within the cell shows as small curved segments, or threads running between and around lipoid droplets,

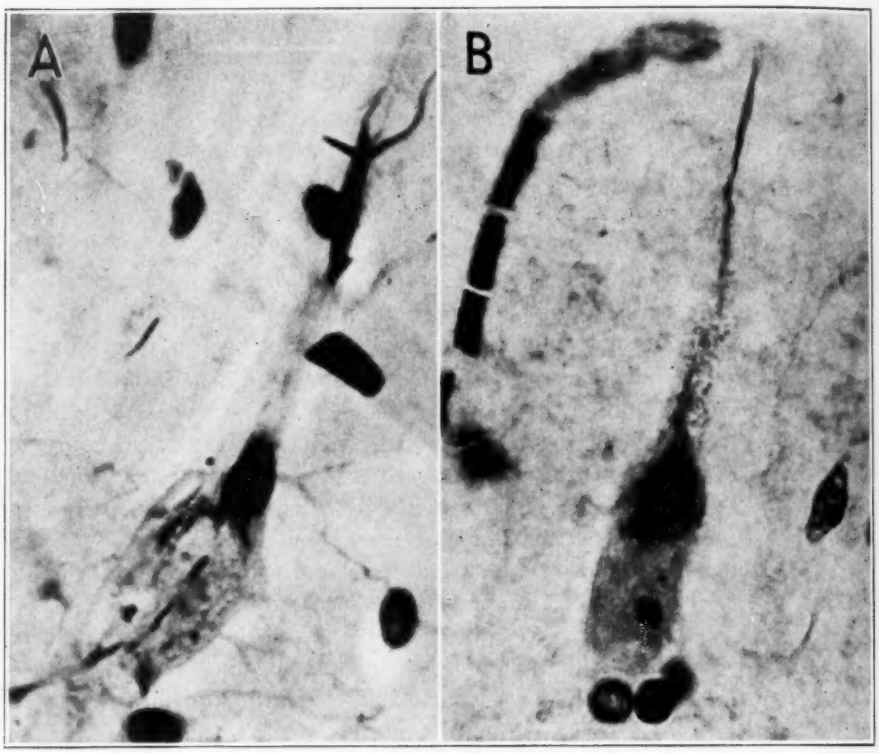

Fig. 5.—Two hippocampal cells affected by the Alzheimer change in which the silver-reducing material is clearly related to preexisting neurofibrils. Both *A* and *B* show cells in which the altered strands are discontinuous, although the neurofibrillar substance is not altered thereby. × 1,000.

and represents a plasmatic framework that, by pathologic change, has acquired the ability to reduce the silver salt. Under the microscope, the plane of focus of which may be altered, these small arcs are seen to be

6. Bielschowsky, M.: (*a*) Zur Kenntnis der Alzheimerschen Krankheit (präsenilen Demenz mit Herdsymptom), J. f. Psychol. u. Neurol. **18**:273-292, 1911; (*b*) Beiträge zur Histopathologie der Ganglienzelle, ibid. **18**:513-521, 1911.

largely continuous with one another and to pervade the lipoid portion of the cell to considerable depth. In addition, the cell in figure 6 *A* shows larger and irregular silver masses in the cytoplasm, which bear a more indefinite relation to the lipoid.

An unusual type of change is seen in figure 2 *C*, in which a crisscross of silver-reducing strands forms a veritable network, with definite and fairly regular interstices. At times such cells appear like a fenestrated membrane, with more or less spherical, yellowish globules suggesting lipoid within the fenestrations. This type appears to be a more advanced stage of that shown in figure 6.

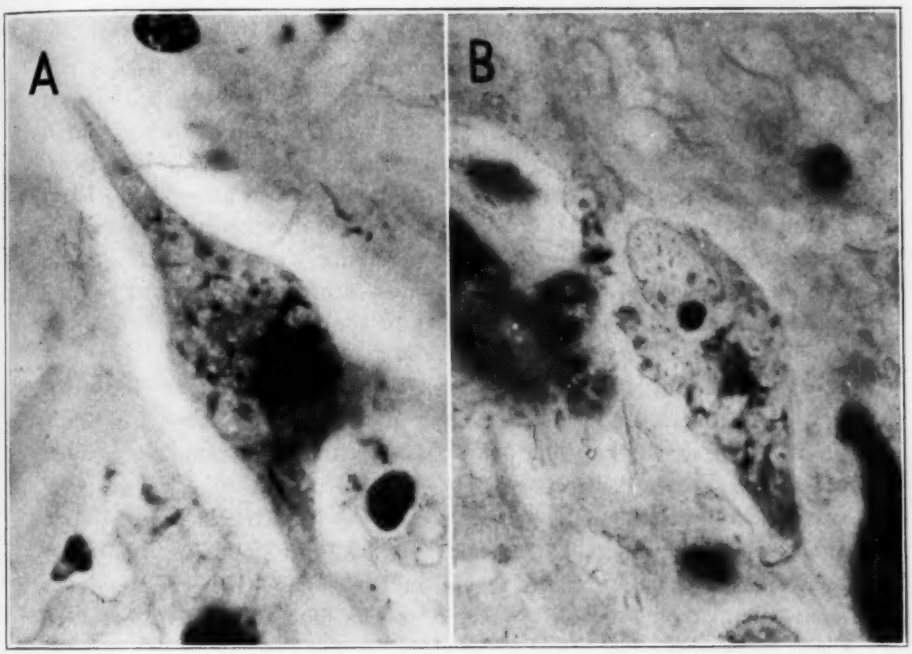

Fig. 6.—Two cells from the pyramidal cell band of the hippocampus, in both of which there is silver-reducing material with no relation to neurofibrils. The cells are crammed with lipoid droplets, and the plasmatic framework in which the lipoid is embedded contains silver-reducing particles appearing as short curved lines. Neurofibrils are known to be absent in the portions of ganglion cells crammed with lipoid. In *B* the cell contains, in addition to the lipoid and the Alzheimer threads, several small granules in vacuoles, the so-called granulovacuolar degeneration. × 1,200.

The known absence of endofibrils in the lipoid portion of the cell precludes the interpretation that this argyrophilic material is neurofibrillar. Other cell forms not containing lipoid also show silver deposits, which, from their morphologic character, are presumably not neuro-

fibrils. In figure 2 *A* the upper part of the cytoplasm is crammed with short dark threads crossing each other in helter-skelter arrangement, appearing like random scratch marks made with pen and ink. In the upper left portion of figure 3 *B* a similar cell is seen under much lower magnification. This crowded random arrangement of pathologic silver-reducing material appears to be in a quite different category from that in relation to endofibrils already illustrated.

Other types of change suggesting the same conclusion are common in the neocortex as well as the hippocampus. A tight argyrophilic ball (fig. 2 *B*) in the paranuclear region is the predominating alteration in the granule cells of the fascia dentata but is observed as well in the hippocampal pyramids. A somewhat comparable change appears in figure 4 *C*, in which the faint outline of a nerve cell body encloses at one end a convoluted, twisted argyrophilic mass, not unlike a misshaped pretzel. Nearby is a much larger, more convoluted and heavier edition of the same change. But in the latter structure no cell body is present. The original twisted mass had, presumably, continued growing, to burst through the confines of the cytoplasm, which disappeared, leaving an independent, extracellular argyrophilic structure. This process of growth and development of silver-reducing substance may thus occur in the gnarled and twisted forms, as well as in the pyriform cells previously described.

A totally different pathologic form is the granulovacuolar degeneration seen in figure 4 *B*. This alteration was first described for senile brains by Simchowicz,[1a] who noted that only the hippocampus contained such cells. They are characterized by small or medium spherical granules surrounded by a clear halo. In the present study such cells are distinctly stained by the simple technic employed and are found to be rather numerous in the cases of more severe senile changes. The small granules stain pale lilac or gray with silver and are of much less intense reaction than the Alzheimer strands, which stain black. These granules may be few in any given cell, or they may be extremely numerous; they may exist by themselves or may coexist in association with the Alzheimer change in the same cell, as seen in figure 6. They are generally considered to be degenerative, and are included here because of their mild silver-reducing capacity.

Senile Plaques.—Fischer [7] long ago published a rather complete description of the various types of plaques stained by the Bielschowsky technic, and little that is new in morphologic description has since been added. Much controversy, however, has centered on the problem of the

7. Fischer, O.: Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz, Monatschr. f. Psychiat. u. Neurol. **22**:361-372, 1907; footnote 3.

derivation and intrinsic nature of these structures. Various authors have implicated nerve cells, microglia cells, astrocytes and oligodendrocytes as the source of the plaques, while others have denied that cellular elements are directly concerned. Cells, for example, have been regarded as secondarily, or even fortuitously, involved in the plaque formation, which is said to be a deposition of foreign substance, either endogenous or exogenous. Several recent papers have discussed these aspects, and it is not necessary to consider them here.

The technical method used in the present study shows all the types of plaques described in the literature. Because normal axis-cylinders are not stained, the plaques stand out from the background with great clarity. In the hippocampus the overwhelmingly predominant type is the diffuse, fine-fibered plaque (fig. 4 *D*), in which there is infiltration of the tissue by a dense pile of delicate threadlike masses (group 8 of Fischer). Ordinary Bielschowsky preparations tend to suppress this fine-fibered plaque, for, as already noted by Fischer and Alzheimer, this type appears most distinctly when axis-cylinders do not stain. The plaque most common in the neocortex, with its complex structure of a central core, or nucleus, a clear space and a surrounding corona, or peripheral portion, is distinctly in the minority in the hippocampus.

Senile plaques, like Alzheimer strands, contain intrinsic reducing substances. The unstable ammoniacal silver solution is dissociated and the silver deposited directly on these structures, without further chemical treatment. Glial cytoplasm is not ordinarily stained, although occasional fibers in these senile brains may also show silver-reducing properties. The method thus offers opportunity to consider the disputed problem of participation of glia in the formation of plaques. If plaques are formed from the different glial types, transitional forms between altered glia cells and the plaques should be evident. It can be categorically stated that this is not the case. In no instance, of the many thousand plaques examined, have the glia cells in and near the plaques shown any reducing power in their cytoplasm. The nuclei are distinct, as they are in any tissue treated by this method, but the cytoplasm does not stain and shows no sign of elaborating or including argyrophilic material. The occasional astrocyte fibers that do stain with this method, as seen in figures 3 and 4 *C*, have an entirely random distribution, bear no special relation to plaques and are not relevant to the present problem.

Entirely different is the question of participation of nerve cells. In the most recent paper on the subject, Soniat [8] claimed that Alzheimer cells may become transformed into senile plaques. The present study, using a quite different technic, offers considerable evidence on this

8. Soniat, T. L. L.: Histogenesis of Senile Plaques, Arch. Neurol. & Psychiat. **46**:101-114 (July) 1941.

point. Frequently a well formed Alzheimer cell is partly or completely surrounded by a characteristic threadlike plaque structure, as seen in figure 4 *A*. The identity of the cell is so well preserved and the fibrillar structure so entirely self contained that a transformation of cell into plaque seems quite out of the question. The process seems to be a deposit of plaque material merely in close apposition to the cell. On the other hand, many Alzheimer cells are seen, as in figure 1 *C* and *D*, in which the endocellular material is not self contained, but frays out beyond the cell confines, and is in intimate association, and even connection, with plaquelike material surrounding the cell in small quantities. Sometimes structures are observed which cannot be classified with certainty. They may be severely disintegrated Alzheimer cells or small plaques. Or, indeed, they may be both; that is, severely disintegrated cells may be identical with small plaques.

However, this is an uncommon observation. These masses, the nature of which is obscure, are invariably small and always located within the pyramidal cell band. The threadlike plaques are widely distributed, are large, infiltrate the tissue diffusely and are often located where participation of ganglion cells is out of the question. Consequently, although some plaques probably arise from or in connection with degenerating Alzheimer cells of the pyriform type, the great majority of plaques come into being independent of this cellular alteration. The "explosion" of Alzheimer cells to form plaques, as suggested by Soniat, has not found support from the present studies on the hippocampus.

Blood Vessels.—The deposition of argyrophilic material in intimate association with blood vessels takes two forms: One is the perivascular plaque, which has been especially described and analyzed by Bouman.[9] An example of this type appears in figure 7 *A*. In a small proportion of cases plaque material is laid down around small vessels, generally of precapillary size. The vessel walls, however, are intact, and the plaque material seems closely applied to the adventitia.

Of a quite different nature is the alteration depicted in figure 7 *B*. Here the blood vessel wall is greatly thickened and the normal constituents are replaced by a dense feltwork of argyrophilic fibers entirely different from reticulin. Bielschowsky [6] briefly mentioned such changes in non-nervous elements and expressed the belief that the vessel walls were impregnated with "Alzheimer substance." More recently Scholz [10] investigated vascular disease in the brain and described at length certain

9. Bouman, L.: (*a*) Ueber die Entwicklung der senilen Plaques, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:267-274, 1925; (*b*) Senile Plaques, Brain **57**:128-142, 1934.

10. Scholz, W.: Studien zur Pathologie der Hirngefässe: II. Die drusige Entartung der Hirnartenerien und -capillaren, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:694, 1938.

argyrophilic changes in the vessel walls. These vascular alterations require further study. They are considered here because their striking silver-reducing power renders necessary a comparison with the Alzheimer change and senile plaques.

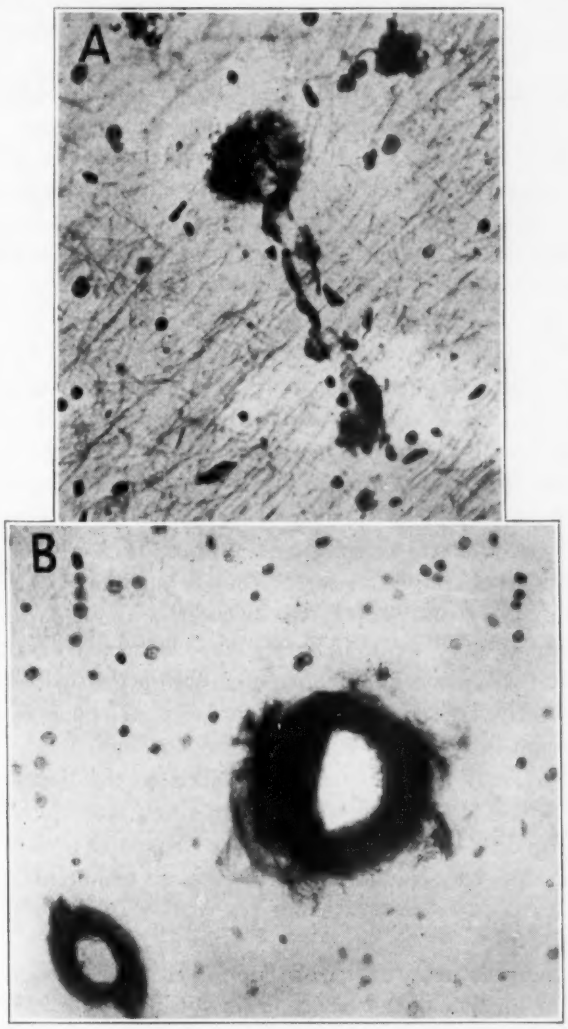

Fig. 7.—*A*, a perivascular plaque with the plaque material closely applied to the vessel wall, which itself does not appear significantly altered. × 300. *B*, two small blood vessels the whole thickness of whose wall is replaced by very strongly silver-reducing material. Morphologically this material is entirely distinct from either plaque substance or reticulin. × 400.

Other Structures.—The staining method employed for the present study brings out corpora amylacea as dark gray, spherical bodies. In

addition, numerous short glial fibrils, as well as focal thickenings of nerve fibrils, together with club, ball and loop formations, are well stained, although normal axis-cylinders are left essentially unstained. The low power photographs (figs. 3 and 4 *C*) show numerous short, dark-staining fibrils which are capable of reducing the ammoniacal silver. However, no morphologic features not already described by other authors can here be added.

A change which to my knowledge has not hitherto been described affects the ependymal cells lining the temporal horn of the lateral ventricle. Short intraepithelial fibrils are frequently seen, with no relation to the subependymal glial feltwork. These intracytoplasmic threads stand out sharply after simple impregnation with silver carbonate and evidently have high reducing power. These structures require further study before an extended description can be given.

COMMENT

The pyriform type of Alzheimer cell change brings up many points of interest. In what is interpreted as the early stage all the fibrillae are delicate, relatively straight and not convoluted. In different, and presumably later, stages some twisting and breaking up are observed; in many cells there is some thickening of the fibrils, but in others extreme delicacy persists after the dissolution of the cell outlines and fine fibrils extend into the interstitial tissue. This is in sharp contrast to the sequence commonly observed in the neocortex and less frequently in the hippocampus (fig. 4 *C*), in which the Alzheimer strands become progressively thicker and more convoluted until a gnarled, knotted mass results and survives the disappearance of the cell. In general, the thinner and less prominent Alzheimer strands are considered an early stage, while the accretion of more argyrophilic material as the disease progresses renders the individual strands thicker and more convoluted. Why in many pyriform cells the delicacy of fibers persists is at present an insoluble question. The close similarity and transitions to fine-fibered, hairlike plaques are facts to be recorded, but speculation on the subject seems unprofitable.

Another unusual feature of the pyriform cell is the change sometimes induced in the immediate cell environment. In *A* and *B* of figure 3 are seen various intensely argyrophilic fibers which are intimately applied to the cell body but which are entirely extracellular. It appears as though argyrophilia within the neuron sometimes induces a comparable alteration in the immediately surrounding interstitial tissue. Just as in supersaturated solutions one crystal provokes the deposition of others around it, so in senile brains one focus of argyrophilic material may cause the deposition of more argyrophilic substance on immediately surround-

ing fibrils. This view, which is only tentatively suggested, implies that the tissue fluids contain material which either is deposited on preformed structures or is left free in glial interstices. This is perhaps comparable to the *plaquefähig Stoffe* of von Braunmühl [11] or the "Alzheimer substance" mentioned by Bielschowsky. There is further implication that the endocellular and the extracellular argyrophilic material are in essence similar, although not identical.

The endocellular silver-reducing material, known commonly as Alzheimer strands, has given rise to much speculation. Von Braunmühl cited Bozler's experiments on nerve cells of invertebrates, in which altering the fluid environment caused tangling and thickening of neurofibrils. According to von Braunmühl, the Alzheimer strands represent an imbibition phenomenon of the ultramicroscopic precursors of the endofibrils. Through the colloidal change of environment the fibrils become thickened and matted and show serpentine twistings because the containing space is too small. He constructed models of the Alzheimer change by treating crude rubber with benzene and stated the belief that the resulting physical system offers an analogy to the pathologic process seen in brain tissue.

It has been a mooted question whether the intracellular argyrophilic substance which most often appears in fibrillar form is really neurofibrillar. Bielschowsky first pointed out that argyrophilic material may first be evident in parts of cells in which no neurofibrils exist. This fact has been abundantly confirmed in the present study with the use of a different staining method. Again, frequently the silver-reducing substance is deposited in forms which bear no relation to neurofibrils. It seems plausible to me that the so-called Alzheimer change represents silver-reducing material which is sometimes laid down on a framework of neurofibrils but at other times may be deposited entirely independently of these structures. This is essentially the eclectic viewpoint expressed by Spielmeyer [1b] and seems preferable to the unitarian hypothesis of von Braunmühl.

The nature and origin of this pathologic material remain unsettled. Whether it is a deposition of foreign substance (the *Einlagerung* of von Braunmühl) or an endocellular product or both is not a fruitful point of discussion. The suggestion has already been tentatively offered that it is in essence similar to the extracellular argyrophilic substance, but probably largely or entirely endocellular in origin. However, conclusive evidence has not yet been presented.

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11. von Braunmühl, A.: (*a*) Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderung. Das hysteretische Syndrom als cerebral Reaktionsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:1-54, 1932; (*b*) Die psychischen Störungen des Rückbildungsalters, ibid. **167**:78, 1939.

SUMMARY

The present communication is devoted to the study of the hippocampal formation in senile brains. The characteristic pathologic change is the presence of intracellular and extracellular substance or substances capable of reducing ammoniacal silver solutions without further chemical treatment. The staining method employed in the present study differs from the usual histologic methods in clearly differentiating such material from technical artefacts and from silver deposits of unknown nature, as well as from normal tissue constituents. The Alzheimer fibrillary change is a generic name for various types of intracellular alteration, all of which have in common this property of a reducing substance. The Alzheimer change represents at least two different processes, in one of which the reducing substance is associated with neurofibrils and in the other of which it is not so associated.

Several types of each process are illustrated and described. Special interest is centered on the pyriform cells in the pyramidal layer, in which the fibrils are sometimes of extreme delicacy even though the cells may be undergoing dissolution. Pericellular argyrophilic structures, in intimate relation to many pyriform cells, are described. Some of this pericellular material is indistinguishable from that form of senile plaque known as the fine-fibered, hairlike type. Examples of transitional stages between pyriform cells and fine-fibered plaques are described, but these form only a small proportion of all plaques. No transition between any other type of plaque and any other type of cell change has been observed. Glia cells do not form or elaborate the material constituting senile plaques. Other types of silver-reducing substances observed in senile brains include short stretches of nerve and glial fibers, often in small groups and clusters; corpora amylacea; granulovacuolar degeneration of neurons, an argyrophilic change in blood vessel walls and an intraepithelial network of fibers in ependymal cells. The interrelation of different types of pathologic silver-reducing substances is briefly discussed.

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DELAYED TRAUMATIC INTRACEREBRAL HEMORRHAGE

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The syndrome of delayed traumatic intracerebral hemorrhage, or *traumatische Spätapoplexie,* was first described in 1891 by Bollinger,[1] who stated that even a mild injury to the head might be followed by the development of foci of softening in the cerebrum or medulla, alterations in the blood vessel walls and intracranial hemorrhage. The syndrome has not aroused a great deal of interest during the fifty years that have elapsed, but there have been occasional reports of the onset of hemiplegia or other evidences of cerebral damage days, or even weeks, after what appeared to have been a slight injury to the head.

In spite of some controversy, both with respect to the exact mechanism of the hemorrhage and its relationship to preexisting vascular disease, delayed traumatic apoplexy has come to be regarded as a disease entity. The symptoms may resemble those of ordinary cerebral hemorrhage, embolism or thrombosis or those seen in cases of brain tumor, rupture of an intracranial aneurysm or subdural hematoma, and the differential diagnosis is important because of therapeutic and medicolegal considerations. In order to justify the diagnosis, however, there must be a definite history of injury, usually without skull fracture. There must be an interval of at least several hours between the trauma and the onset of symptoms. Other causes of hemorrhage or thrombosis, especially arteriosclerosis, hypertension, syphilis, nephritis, alcoholism or other toxic or inflammatory conditions, must be eliminated. To assure a conclusive diagnosis, a pathologic examination or surgical evidence is necessary.

The following 2 cases illustrate the syndrome.

From the Department of Neurology, the University of Michigan Medical School and University Hospital.

Read at the Twentieth Annual Meeting of the Central Neuropsychiatric Association, Ann Arbor, Mich., Oct. 25, 1941.

1. Bollinger, O.: Ueber traumatische Spät-Apoplexie: Ein Beitrag zur Lehre von der Hirnerschütterung, in Internationale Beiträge zur wissenschaftlichen Medicin, Festschrift, Rudolf Virchow gewidmet zur Vollendung seines 70. Lebensjahres, Berlin, A. Hirschwald, 1891, vol. 2, pp. 457-470.

REPORT OF CASES

CASE 1.—R. C. Jr., a man aged 27, received a slight injury behind the right ear when he was struck by a board, and after this he noted a mild headache for about one hour. Twenty-four hours later the headache recurred, followed in a few hours by nausea, vomiting and generalized weakness. These symptoms continued unabated for six days, when the headache increased in severity and right hemiplegia and aphasia developed.

At the time of admission to the University Hospital the patient had complete right hemiplegia, with palsy of the right side of the face. He responded poorly, but in spite of this aphasia could be demonstrated. There were rigidity of the neck and suggestive Kernig and Brudzinski signs. The blood pressure was 144 systolic and 80 diastolic. There was papilledema bilaterally. The Kahn reaction of the blood was negative. Spinal puncture showed a pressure of 380 mm. of water with no block, and the spinal fluid contained 11,280 red blood cells per cubic millimeter.

An exploratory trephination and a ventriculographic examination were performed on the day of admission. In both frontal openings there was considerable dural bleeding, but the cerebral cortex appeared to be normal. The ventriculogram showed questionable displacement of the ventricles to the right. The following day the patient appeared to be slightly improved, but the next day his temperature rose and respiratory distress developed. Death occurred forty-eight hours after the operation.

Autopsy.—The brain was large and edematous, weighing 1,520 Gm. The left hemisphere was larger than the right and was soft. The leptomeninges were thin, and the basal vessels were delicate. There were evidences of extravasated blood over the dura and under the arachnoid over the surface of the brain. Recent hemorrhages into the meninges were present in the region of the chiasm, at the base of the pons, in the left sylvian fissure and around both anterior cerebral arteries. All the hemorrhages were superficial and surrounded large vessels. Coronal sections of the brain showed extensive necrosis of the posterior portion of the left frontal lobe, most of the insula and the anterior part of the left parietal lobe. The right hemisphere, as well as other parts of the brain, was moderately hyperemic but otherwise normal (fig. 1).

Histologic Examination.—No thrombi or emboli were noted. There was severe acute ischemic degeneration of the neurons in the aforementioned areas, with almost complete destruction of the gray matter. Slight glial activity was evident. There were edema of the meninges and perivascular petechial hemorrhages of recent origin. Tissue response was limited to slight perivascular lymphocytic infiltration, with a few gitter cells. The blood vessel system was normal. No changes were noted in the brain stem or cerebellum.

CASE 2.—K. S., a woman aged 56, was well until Oct. 17, 1939, when she fell down a flight of twenty steps and suffered a compression fracture of the ninth dorsal vertebra. She was unconscious for about two minutes after the fall and was dazed for fifteen to twenty minutes. She was admitted to the University Hospital the next day, and at this time the physical and neurologic examinations showed no abnormalities aside from a few ecchymoses; there was no evidence of involvement of the spinal cord. On the evening of October 21, four days after the fall, it was noticed that the patient's conversation was incoherent and that her speech was slurred. A few hours later she lost consciousness and complete left hemiplegia developed.

Examination after the development of the hemiplegia showed the patient to be stuporous, responding slightly to painful stimuli. The ocular fundi were normal, without papilledema. There were palsy of the left side of the face and paralysis of the left side of the body. The blood pressure was 130 systolic and 80 diastolic. Spinal puncture showed a pressure of 200 mm. of water with no block; the spinal fluid had a ground glass appearance and contained 1,000 red blood cells per cubic millimeter. A roentgenogram of the skull was interpreted as normal. The Kahn reaction of the blood was negative.

The patient became more deeply stuporous, and on October 23, two days after the onset of the paralysis, trephination was done. The dura was of normal color

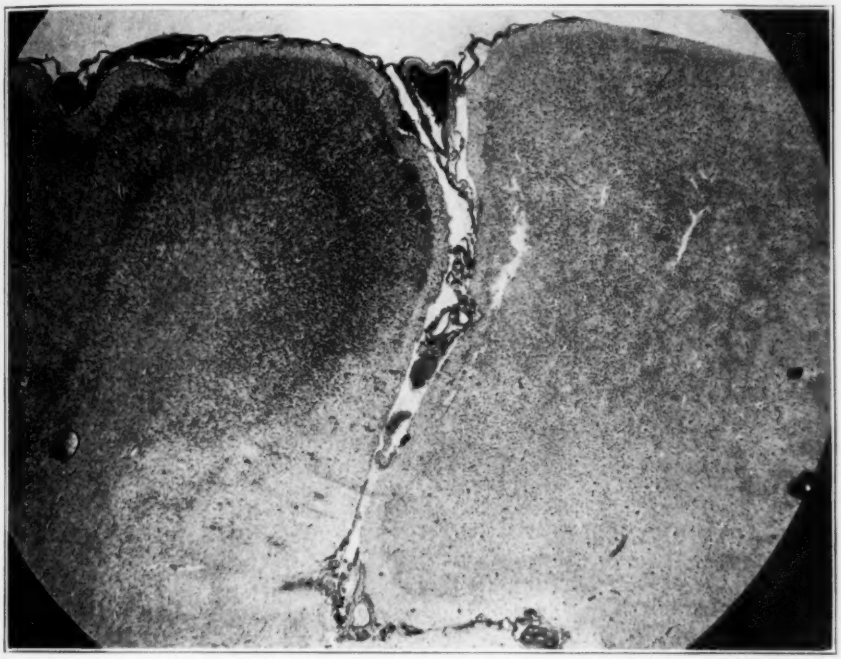

Fig. 1.—Section of the posterior portion of the left frontal lobe and the anterior portion of the left parietal lobe, showing ischemic degeneration of the neurons and beginning necrosis (case 1).

bilaterally, and there was no evidence of subdural hematoma. When the dura was retracted from the brain on the right side a small amount of dark red blood escaped. A needle was passed into the right lateral ventricle, and blood was obtained. The patient responded slightly after the operation, but later progressive paralysis of the upper and lower extremities developed on both sides. On October 25, two days after the trephination, she died.

Autopsy.—Postmortem examination was limited to the head and central nervous system. Examination of the skull showed a linear fracture involving the inner table of the right parietal bone and the posterior portion of the petrous

ridge of the right temporal bone. The blood vessels showed no signs of atherosclerosis, and there were no thrombi. The brain weighed 1,380 Gm. The right hemisphere was larger than the left, and a massive hemorrhage, measuring 5 by 2.5 by 7 cm., involved the white matter of the anterior portion of the right parietal and temporal lobes, the anterior portion of the knee of the right internal capsule and the putamen, globus pallidus and claustrum, as well as the capsula externa and capsula extrema (fig. 2), on the right side. There was a patchy subarachnoid hemorrhage, especially over the right hemisphere, and diffuse ischemic changes were present in the cortex outside the area of hemorrhage. The white matter at the base of the right temporal lobe and the upper portion of the right parietal lobe was intact. The lateral ventricle on the right was filled with blood. The interventricular foramen was blocked, but the third ventricle, the

Fig. 2.—Section of the right parietal and temporal lobes after the removal of the clot, showing extensive area of degeneration.

aqueduct and the fourth ventricle were patent. The left cerebral hemisphere and the cerebellum were grossly normal. There were a few scattered hemorrhages in the dorsal portion of the pons.

Histologic Examination.—The brain tissue in the area of hemorrhage was necrotic. There were countless perivascular ring hemorrhages, which coalesced to form the massive extravasation of blood. Around the periphery of the hemorrhage were multiple small ischemic foci. Histologic examination of the blood vessels showed only moderate thickening and sclerosis, corresponding to the age of the patient. There were moderate perivascular accumulations of lymphocytes and fat-containing gitter cells, but no changes were observed in the blood vessel walls.

In the first case there was transient headache followed by a latent period of twenty-four hours, when the headache recurred. The more

severe cerebral symptoms did not become manifest until six days later, and death occurred nine days after the trauma. In the second case there was a latent period of about ninety-six hours between the injury to the head and the onset of cerebral symptoms, although transient loss of consciousness occurred immediately after the accident. Death occurred four days after the onset of the symptoms and eight days after the injury. This development of the clinical picture is fully in accord with the conclusions of Bollinger [1] and others, who stated that there may be a latent period of hours, days or even weeks between the injury and the onset of symptoms.

COMMENT

Bollinger's [1] original conclusions regarding the nature and cause of delayed traumatic apoplexy were based on the observations of Duret,[2] who, in 1878, published a study on the experimental and clinical sequelae of cerebral trauma. The latter, by means of blows on the head and injections of fluid into the cranium of experimental animals, had produced lacerations and foci of softening in the region of the lateral ventricles, the aqueduct of Sylvius and the fourth ventricle. He expressed the opinion that trauma to the head compressed the lateral ventricles, driving the cerebrospinal fluid into the third and fourth ventricles. This rush of fluid caused lesions at the sites of constriction, namely, the aqueduct and the fourth ventricle. This work was repeated by Gussenbauer.[3]

Postmortem examination of the patients observed by Bollinger showed lesions similar to those produced by Duret. In all 4 patients there were dilatation of and hemorrhage into the aqueduct and the fourth ventricle or foci of softening and hemorrhage in the brain stem. Bollinger expressed the belief that even a mild head injury might be followed by degeneration and necrosis in the cerebrum or the brain stem. This, in turn, might produce alterations in the blood vessel walls which would result in hemorrhage, due in part to alteration in the walls, but also to weakening of the tissues immediately surrounding the vessels and to a relative increase in the arterial pressure.

Bollinger's work was criticized by various authors, especially by Langerhans,[4] who stated that none of Bollinger's cases could be called instances of delayed traumatic apoplexy. In the first case there was a

2. Duret, H.: Etude sur l'action du liquide céphalo-rachidien dans les traumatismes cérébraux, Arch. de physiol. norm. et path. **5**:183, 1878.

3. Gussenbauer, C.: Ueber Mechanismus der Gehirnerschütterung, Prag. med. Wchnschr. **5**:1 (Jan. 7); 15 (Jan. 14); 23 (Jan. 21) 1880.

4. Langerhans, R.: Die traumatische Spätapoplexie, Berlin, A. Hirschwald, 1903.

fracture of the skull with meningeal hemorrhage, and only a meager report of the other findings was given; in the second no definite area of softening or traumatic degeneration was observed; in the third there was a close temporal relation between the injury and the hemorrhage, and in the fourth no microscopic examination of the isthmus was made. Langerhans expressed the belief that in all cases of post-traumatic apoplexy the hemorrhage is due to preexisting vascular disease. Other studies on the syndrome, however, especially those of Stadelmann,[5] Mendel,[6] Allen,[7] Singer [8] and Eck,[9] led to the conclusion that delayed traumatic apoplexy is a disease entity, so that, in spite of criticism, Bollinger's concept has survived. There have been many debated points, however. Among them are the exact mechanism of the hemorrhage, its mode of onset and its relationship to preexisting vascular disease. Other controversial issues are the possible mechanical effects of the trauma on the intracranial structures, especially the arteries, and on the cerebrospinal fluid pressure and the relationship of the hemorrhage to a secondary rise in the intra-arterial pressure or to normal pressure within traumatized arteries.

Marie and Crouzon [10] expressed the belief that in all cases of delayed traumatic apoplexy there is evidence of preexisting vascular disease, and Wechsler [11] also stated that arteriosclerosis is present in all cases and that trauma should be considered only a precipitating or exciting factor and not the ultimate cause of the syndrome. Warrington [12] expressed the opinion that in most instances there is evidence of preexisting vascular disease, in accord with Langerhans' statements, but that in a rare type of delayed traumatic apoplexy injury may result in hemorrhage in the absence of such disease.

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5. Stadelmann, E.: Ueber Späterkrankungen des Gehirns nach Schädeltraumen, Deutsche med. Wchnschr. **29**:95 (Feb. 5); 117 (Feb. 12) 1903.

6. Mendel, K.: Der Unfall in der Aetiologie der Nervenkrankheiten: III. Die traumatische Spätapoplexie, Monatschr. f. Psychiat. u. Neurol. **22**:264, 1907.

7. Allen, A. R.: Delayed Apoplexy (Spätapoplexie), with a Report of a Case, J. Nerv. & Ment. Dis. **35**:763 (Dec.) 1908.

8. Singer, K.: Die sogenannte traumatische Spätapoplexie, Ztschr. f. d. ges. Neurol. u. Psychiat. **75**:127, 1922.

9. Eck, H.: Beitrag zur Lehre der traumatischen Spätapoplexie, Virchows Arch. f. path. Anat. **284**:67, 1932.

10. Marie, P., and Crouzon, O.: De l'apoplexie tardive traumatique, Rev. de méd., Paris **25**:368, 1905.

11. Wechsler, I. S.: A Text-Book of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1931, p. 521.

12. Warrington, A. B.: Traumatic Delayed Apoplexy, Rev. Neurol. & Psychiat. **8**:277, 1910.

According to Michel,[13] Mazurkiewicz,[14] Kron[15] and many of the older writers, the essential pathologic change leading to the hemorrhage is an alteration of the blood vessel walls accompanying foci of degeneration and softening in the cerebrum. The vascular proliferation and the perivascular infiltration and softening, with resulting disturbance in nutrition of the blood vessel walls and weakening of the tissues surrounding the blood vessels, lead to the rupture of the artery and the ictus. As a consequence, in older persons, whose vessels are less resistant, even minor injuries can cause hemorrhage. Stadelmann[5] expressed the belief that a disturbance in circulation always precedes the softening, while Mendel[6] stated that an area of perivascular softening causes fatty degeneration in the blood vessel walls and this is followed, in turn, by the development of miliary aneurysmal dilatations or arteriosclerosis. Marburg[16] stated that damage to the vessel walls at the time of injury leads to progressive change, which finally results in rupture of the vessel and hemorrhage. Rosenhagen[17] expressed the belief that concussion leads to circulatory disturbances of the cerebral vessels, and these in turn bring about the hemorrhage.

Allen[7] asserted that trauma to the brain produces mechanical agitation of the brain substance, especially of the arteries, which are filled with an incompressible fluid. The location of the major action on the vessels is determined by the direction of the force of the blow to the head. Immediately after the injury there is generalized vasoconstriction of the cerebral arterial system, and this is followed by paresis of the vessel walls. The injured vessels undergo endothelial proliferation; thrombotic processes are set up, and the ictus takes place. The delayed apoplexy may be the result either of hemorrhage or of thrombosis. The symptoms are produced by injury to the vessel wall and not by necrotic softening around the arteries or by change in the cerebrospinal fluid pressure. Miller,[18] however, expressed the belief that the effect of the impact on the cerebrospinal fluid is important. Friedman[19] claimed

13. Michel, E.: Ein Beitrag zur Frage von der sogenannten traumatischen Spätapoplexie, Wien. klin. Wchnschr. **9**:789 (Aug. 27) 1896.

14. Mazurkiewicz, J.: Ein Fall von traumatischer Spätapoplexie, Jahrb. f. Psychiat. u. Neurol. **19**:553, 1900.

15. Kron, H.: Zur Frage der traumatischen Spätapoplexie, Deutsche med. Wchnschr. **29**:656 (Sept. 10) 1903.

16. Marburg, O.: Zur Frage der Hemorrhagia cerebri bei jüngeren Menschen und deren differentieller Diagnose, Deutsche Ztschr. f. Nervenh. **105**:22, 1928.

17. Rosenhagen, H.: Ueber postkommotionelle Veränderungen im Gehirn, Deutsche Ztschr. f. Nervenh. **114**:29, 1930.

18. Miller, A. H.: A Case of Late Traumatic Subdural Haemorrhage: Traumatic Late Apoplexy, Lancet **2**:1339 (Nov. 6) 1909.

19. Friedman, E. D.: Massive Intracerebral Hemorrhage of Traumatic Origin, in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1940, pp. 123-132.

that the hemorrhage is the result of diapedesis and escape of blood into the tissues of the brain.

Courville and Blomquist [20] have recently made a detailed study of the pathogenesis of traumatic intracerebral hemorrhage, especially as related to delayed traumatic apoplexy. They expressed the belief that the hemorrhage is always the result of the coup-contrecoup mechanism and that the injury must be sustained while the head is in motion. It is probable that an injury resulting from a blow to the head at rest will not cause a hemorrhage within the brain substance unless there is serious disease of the blood vessels. They stated that the hemorrhage is brought about by one of three processes: (1) development of foci of necrotic softening in the brain as a direct result of the trauma; (2) preexisting alterations in the vessel walls; or (3) delayed hemorrhage in a focus of primary hemorrhage which occurred at the time of the injury.

In our cases there was no evidence of vascular disease that might be interpreted as an etiologic factor, and no alterations were observed in the arterial walls that might have taken place after the injury. The essential pathologic change seemed to be that of infarction, either anemic or hemorrhagic, and both varieties have been demonstrated. Inasmuch as evidences of atherosclerosis, embolism and thrombosis were not noted, it is believed that the pathophysiologic mechanism was undoubtedly that of vascular spasm, secondary to trauma, leading first to anemic infarction, with resulting liquefaction necrosis and local death. This is the picture seen in the first case. In the second case there was hemorrhage into the necrotic area, with resulting hemorrhagic infarction. This type of spasm may occur in either normal or pathologic vessels, but probably takes place with less stimulation or trauma in the latter.

It appears to be fairly well accepted that delayed traumatic apoplexy may occur, even though certain observers (Courville and Blomquist [20]) have expressed doubt as to its frequency. Oppenheim [21] pointed out that caution must be exercised in making the diagnosis, so that a spontaneous hemorrhage will not be confused with a traumatic one, but he expressed the belief that the concept of traumatic late apoplexy is valid. Russell [22] stated that delayed intracerebral hemorrhage is an important, though rare, complication of head injury. Certain criteria were stressed by Singer,[8] Stadelmann [5] and others as necessary to the

20. Courville, C. B., and Blomquist, O. A.: Traumatic Intracerebral Hemorrhage, with Particular Reference to Its Pathogenesis and Its Relation to "Delayed Traumatic Apoplexy," Arch. Surg. **41**:1 (July) 1940.

21. Oppenheim, H.: Text-Book of Nervous Diseases, translated by Alexander Bruce, London, T. N. Foulis, Publisher, 1911, vol. 2, p. 795.

22. Russell, W. R.: Late Effects of Head Injury, Tr. Med.-Chir. Soc. Edinburgh, 1938-1939, p. 88; in Edinburgh M. J., July 1939.

diagnosis. The injury to the head must be severe enough to cause definite trauma to the intracranial structures. Loss of consciousness and fracture of the skull are not necessary. The vascular system must be sound at the time of the injury. There must be a latent period during which the patient is symptom free; he may apparently be recovering from the injury at the time of the ictus. The interval between the injury and the development of symptoms should not be less than one day or more than eight weeks. The location of the lesion is not dependent on the site of injury. Increase in the intra-arterial pressure is not a necessary precursor to the hemorrhage.

The cases of delayed traumatic apoplexy that have been reported in the recent literature differ from those described by Bollinger in that the hemorrhage was generally within the cerebrum, with resulting hemiplegia, rather than in the medulla or in the neighborhood of the aqueduct or the fourth ventricle. In none did there seem to be any relation to abnormalities of the cerebrospinal fluid pressure. The spinal fluid occasionally contained blood, but only if there had been associated intraventricular or subarachnoid hemorrhage. Cases with unusual symptoms, such as predominant mental changes, have also been described.[23]

According to Symonds,[24] there are two varieties of delayed traumatic apoplexy. The early one occurs from a few days to a few weeks after the injury, and the clinical picture resembles that seen in cases of ordinary cerebral hemorrhage or of a ruptured intracranial aneurysm. In the late variety, which may occur months to years after a head injury, a chronic intracerebral hematoma develops and the symptoms resemble those seen with brain tumor. In this variety death usually results from hemorrhage into the cystic cavity of the hematoma. Bailey [25] cited three types of apoplexy occurring with head injury: that taking place simultaneously with the injury, and usually associated with preexisting vascular disease; that occurring shortly after the injury, or the usual delayed apoplexy, and that appearing years after the injury, probably the result of slow thrombosis.

Our cases illustrate that head injury may result, even after a latent period, in severe damage to the brain. Inasmuch as alterations of the blood vessel walls, cellular infiltration and changes in blood pressure are not found, it seems justifiable to assume that the degenerative changes and resulting hemorrhage are the result of vascular spasm. It should be emphasized that, as exemplified in case 1, even very mild

23. Keller, W. K., and Miller, A. J.: Posttraumatic Psychosis, Internat. Clin. **4**:136 (Dec.) 1940.

24. Symonds, C. P.: Delayed Traumatic Intracerebral Haemorrhage, Brit. M. J. **1**:1048 (June 29) 1940.

25. Bailey, P.: Traumatic Apoplexy, M. Rec. **66**:528 (Oct. 1) 1904.

trauma may produce infarction, probably resulting from spasm of normal vessels, in a healthy young person. It is probable that instances of delayed traumatic apoplexy occur more frequently than has been assumed.

The recognition of delayed traumatic apoplexy is important not only from a therapeutic but from a medicolegal point of view. The condition must be differentiated from subdural hematoma, ruptured intracranial aneurysm and subarachnoid hemorrhage, and often trephination is necessary in order to make the diagnosis. The prognosis is more grave than that for subdural hematoma and subarachnoid hemorrhage, but the condition is not necessarily fatal. Neurosurgeons have for some years removed the intracerebral hematoma in certain cases of spontaneous cerebral hemorrhage, especially if signs of increasing intracranial pressure are present (Cushing,[26] Russell and Sargent,[27] Penfield,[28] Bagley[29] and Furlow, Carr and Wattenberg[30]), and in cases of the delayed traumatic type successful surgical intervention has been reported by Naffziger and Jones,[31] Craig and Adson,[32] Doughty[33] and Pilcher.[34] From a medicolegal point of view it is important to bear in mind that the syndrome may not be a rare complication following head injury. Even with a latent period of a few days to several weeks there may be a definite etiologic relation between the injury and the apoplexy.

1313 East Ann Street.

26. Cushing, H.: The Blood Pressure Reaction of Acute Cerebral Compression, Illustrated by Cases of Intracranial Hemorrhage, Am. J. M. Sc. **125**:1017 (June) 1903.

27. Russell, A. E., and Sargent, P.: Apoplectiform Cerebral Haemorrhage: Operation; Evacuation of Blood; Slow Improvement, Proc. Roy. Soc. Med. **2**:44 (Jan. 21) 1909.

28. Penfield, W.: The Operative Treatment of Spontaneous Intracerebral Hemorrhage, Canad. M. A. J. **28**:369 (April) 1933.

29. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types, with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133 (May) 1932.

30. Furlow, L. T.; Carr, A. D., and Wattenberg, C.: Spontaneous Cerebral Hemorrhage: The Surgical Treatment of Selected Cases, Surgery **9**:758 (May) 1941.

31. Naffziger, H. C., and Jones, O. W.: Late Traumatic Apoplexy: Report of Three Cases with Operative Recovery, California & West. Med. **29**:361 (Dec.) 1928.

32. Craig, W. McK., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage: Etiology and Surgical Treatment, with a Report of Nine Cases, Arch. Neurol. & Psychiat. **35**:701 (April) 1936.

33. Doughty, R. G.: Posttraumatic Delayed Intracerebral Hemorrhage, South. M. J. **31**:254 (March) 1938.

34. Pilcher, C.: Subcortical Hematoma: Surgical Treatment, with Report of Eight Cases, Arch. Neurol. & Psychiat. **46**:416 (Sept.) 1941.

CURARE AND METRAZOL THERAPY OF PSYCHOSES

REPORT OF A FATAL CASE

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For several years metrazol has been widely used intravenously to produce convulsions in the shock therapy of various psychoses. One of the most important disadvantages of this form of therapy has been the production of injuries by the severe convulsions. These injuries have included fractures of the dorsal vertebrae, femur, pelvis and humerus, as well as dislocations of the shoulder and mandible.[1] Various workers have employed a variety of methods to reduce the severity of metrazol-induced convulsions and consequent injuries. These methods, including the use of restraints, postures, supports, splints and spinal anesthesia, have had some success, but all have important disadvantages.

Bennett [2] first described the use of curare in modifying the metrazol convulsion, and numerous other workers have employed this drug, with excellent results, in preventing injuries due to convulsions.

Curare has been used since the time of Claude Bernard as a laboratory drug for blocking nerve impulses between nerve and striated muscle.[2] Therapeutically it has had some success in the treatment of tetanus [3] and spastic paralysis in children.[4] In laboratory animals

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From the Norfolk State Hospital.

1. Hamsa, W. R., and Bennett, A. E.: Traumatic Complications of Convulsive Shock Therapy, J. A. M. A. **112**:2244 (June 3) 1939. Polatin, P.; Friedman, M. M., and Horwitz, W. A.: Vertebral Fractures Produced by Metrazol Induced Convulsions, ibid. **112**:1684 (April 29) 1939. Bennett, B. F., Jr., and Fitzpatrick, C. P.: Fractures of the Spine Complicating Metrazol Therapy, ibid. **112**:2240 (June 3) 1939. Graves, C. C., and Pignataro, T. P.: Injuries Sustained During the Course of Metrazol Shock Therapy, Psychiatric Quart. **14**:477 (July) 1940.

2. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**:322 (Jan. 27) 1940.

3. West, R.: Intravenous Curare in Treatment of Tetanus, Lancet **1**:12-16 (Jan. 4) 1936.

(Footnotes continued on next page)

receiving lethal doses of curare, the chief action resulting in death is peripheral paralysis of the muscles of respiration, but much larger doses can be administered without fatal results if artificial respiration is employed. McIntyre [5] administered slowly over a twelve hour period as much as one hundred times the calculated lethal dose to a dog given artificial respiration without death from curare poisoning.

As far as we are aware, our case is the only one in which death followed shock therapy with curare and metrazol. We have been unable to find any similar report in the literature, and the manufacturer of the preparation of curare which we use stated that there have been no deaths from this therapy in the course of over 4,000 injections.

REPORT OF CASE

Pretreatment History.—B. K., a white man of Bohemian extraction, aged 20, began to manifest symptoms of mental derangement early in January 1941. He was observed in the CCC dispensary and in the Station Hospital at Fort Meade, S. D., where a tentative diagnosis of schizophrenia was made.

The results of physical examination made there and after his admission to this hospital agreed essentially on everything except the blood pressure, which was 148 systolic and 100 diastolic, at the Station Hospital and 122 systolic and 80 diastolic here. The general physical findings were essentially without significance. He was 67 inches (170 cm.) tall and weighed 138 pounds (62.6 Kg.). He had had no serious illness except appendicitis, for which he underwent appendectomy, with good results, in 1935. Laboratory tests gave normal results at all times.

He was admitted to the Norfolk State Hospital on March 5, 1941, after having been observed for mental symptoms since early in January.

Treatment.—The temperature being 98.6 F., the pulse rate 70 and the respiratory rate 18, treatment was begun. Four cubic centimeters of a preparation of curare,[6] containing the active principle in an amount equivalent to 80 mg. of crude curare, was given intravenously in an interval of slightly over a minute. After approximately one and a half minutes the maximal effects apparently were obtained, as denoted by such signs of partial muscular paralysis as ptosis of the eyelids. Immediately then, 5 cc. of a 10 per cent solution of metrazol was injected intravenously very rapidly, as recommended. After about fifteen seconds the expected shock, moderately softened, occurred with clonic-tonic-clonic convulsion, which lasted exactly one minute. During the convulsion the skin became livid. Immediately on cessation of the final clonic phase there were about a half-dozen rapid gasps for breath, and

4. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**:307-327 (Feb.) 1939. Bennett.[2]

5. McIntyre, A. R.: Personal communication to the authors, April 5, 1941. This experiment was performed on an anesthetized dog, and the quantity of curare was administered over a period totaling about twelve hours. Physostigmine was administered twice during this period. The dog, which had been prepared for records of blood pressure and respiration, was not allowed to survive at the end of the experiment.

6. Intocostrin, manufactured by E. R. Squibb & Sons, New York.

then respiration ceased. Several movements of the larynx were observed, but no breath was heard to pass. Immediately artificial respiration was begun and an oxygen mask applied, and these measures were maintained continuously. Also 1 cc. of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) was given intramuscularly; within two minutes and a few seconds 1 cc. of solution of epinephrine hydrochloride U. S. P. was given intracardially. Administration of these drugs was repeated at about two minute intervals, without results. The pulse in the meantime was noted to continue at a rate of about 80 per minute, with good volume, for about six minutes and then rapidly began to fail. About two minutes later no pulse could be detected and no heart sounds heard. At one time, about four minutes after the aforementioned measures were begun, it was thought respiration was established, but on cessation of efforts none could be detected. Apparently, within fifteen minutes from the beginning of the treatment all life had ceased. However, we continued to administer stimulants and to employ artificial respiration with oxygen inhalations for a long time before abandoning hope and conceding death.

Autopsy, except for examination of the head, was performed about five hours after death. A few postmortem changes were noted. The lungs showed slight breaking, such as is usually seen after prolonged artificial respiration. Several of the alveoli were ruptured. The trachea and bronchi contained some frothy fluid. The heart weighed 275 Gm., was resting in systole and showed no pathologic change or evidence of trauma. The cortices of the kidneys showed several microscopic abscesses, but apparently function was not impaired. The anatomic diagnosis stated that no pathologic evidence was found to account for death.

COMMENT

Was this death caused by metrazol or curare or both? In most cases of sudden death following metrazol injections (without curare) the cause seems to have been cardiac failure and autopsy has usually revealed cardiac lesions [7]; in other cases death has apparently been due to injury of the brain. Pessin and Reese [8] reported 1 case of death from metrazol shock which was apparently due to respiratory failure, but the patient is said to have had irregular respiration all his life and autopsy showed acute cardiac dilatation. Autopsy in our case showed no evidence of damage to the heart. Unfortunately, we cannot eliminate the possibility of damage to the brain, since examination of the head was not permitted. Our patient's heart action was apparently good for about nine minutes after spontaneous respirations had ceased, and, although other possibilities cannot be entirely eliminated, it is our opinion that he died of respiratory failure due to curare poisoning. The dose of curare administered was somewhat greater than that recommended by the manufacturer, but was about the same as that used in

7. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Fatal Case with Autopsy, J. A. M. A. **112**:310-311 (Jan. 28) 1939.

8. Pessin, J., and Reese, H. H.: Fatal Complication Following Metrazol Treatment for Schizophrenia, Am. J. Psychiat. **96**:393-395 (Sept.) 1939.

similar cases by ourselves and other workers. Prostigmine [2] is said to counteract the effects of curare, but, unfortunately, it was not available at the time this patient was treated.

In spite of our unfortunate experience in this case, we believe that curare is a valuable drug in preventing injuries during shock therapy, and we are continuing its use in selected cases.

SUMMARY AND CONCLUSIONS

A case of sudden death following shock therapy with curare and metrazol is reported.

The probable cause of death is discussed.

In spite of this experience, we believe that premedication with curare is the best available method for the prevention of traumatic accidents during shock therapy. We believe that caution should be used in the dose, especially the first time a patient is treated. Prostigmine should be instantly available for use in counteracting the effects of curare whenever this drug is employed.

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PATHOLOGIC ANATOMY OF HUMAN NERVOUS SYSTEM IN AVITAMINOSIS

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Consequent to a low economic status and inadequate hygienic precaution, China has a high morbidity rate of dysentery, tuberculosis and malnutrition. There have been a number of clinical reports from China (Keefer and Yang,[1] Keefer, Huang and Yang,[2] Yang and Hu,[3] Keefer,[4] Keefer, Huang and Yang,[5] Alexander and Wu[6] and Yang and Huang[7]) on the nervous disorders associated with these diseases, but corresponding neuropathologic descriptions are scanty (Alexander and Wu[8]). In view of this, I present the following series of cases representing a group of Chinese soldiers who died in a poorly equipped Red Cross base hospital in Peiping, China, of dysentery, intestinal tuberculosis or malnutrition. Postmortem examination in these cases revealed an extraordinarily striking and uniform picture, particularly a widespread degenerative process in the nervous system. My intention in reporting these cases is not only to verify the common clinical impres-

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From the Division of Neurology and Psychiatry, Peiping Union Medical College.

1. Keefer, C. S., and Yang, C. S.: Anemia of Undernutrition, Nat. M. J. China **15**:701, 1929.

2. Keefer, C. S.; Huang, K. K., and Yang, C. S.: The Importance of Undernutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, Nat. M. J. China **15**:743, 1929.

3. Yang, C. S., and Hu, C. K.: The Relation of Pellagra to Enteric Disease, Nat. M. J. China **16**:625, 1930.

4. Keefer, C. S.: Some Clinical Aspects of Deficiency Diseases, New England J. Med. **205**:1086, 1931.

5. Keefer, C. S.; Huang, K. K., and Yang, C. S.: Anemia Associated with Chronic Dysentery, Arch. Int. Med. **47**:436 (March) 1931.

6. Alexander, L., and Wu, T. T.: Symptomatic Involvement of the Nervous System in Different Forms of Dysentery, Chinese M. J. **48**:1, 1934.

7. Yang, C. S., and Huang, K. K.: Beriberi in Nanking, Chinese M. J. **48**:20, 1934.

8. Alexander, L., and Wu, T. T.: Cerebral Changes in Gastro-Intestinal Infections with Terminal Cachexia: Histopathologic Studies on Dysentery with Comments on Similar Observations in Intestinal Tuberculosis, Arch. Neurol. & Psychiat. **33**:72 (Jan.) 1935.

sion of neurologic disturbances in these diseases but to clarify some of the pathologic factors in the nerve lesions associated with avitaminosis.

The neuropathologic material consisted of the brain, spinal cord, cranial and spinal nerve roots, dorsal spinal ganglia and peripheral nerve trunks. The specimens were fixed in dilute solution of formaldehyde or 3 per cent U. S. P. (1:10) solution of potassium bichromate and either embedded in pyroxylin or gelatin or not embedded. Besides staining with cresyl violet, hematoxylin and eosin and Herxheimer's scarlet red, the technics of Nissl, Van Gieson, Marchi, Spielmeyer, Schroeder, Bielschowsky, Alzheimer and Mann and Holzer were applied.

REPORT OF CASES

CASE 1.—A Chinese youth aged 19 was admitted to the Red Cross base hospital on Sept. 8, 1937 because of diarrhea and feverishness. There were signs of peritonitis, anesthesia of both legs and feet and stools characteristic of dysentery. The blood culture was sterile, and agglutination tests gave negative results. A clinical diagnosis of tuberculosis of the intestine and peritoneum was made. He died on December 8.

Autopsy.—The general pathologic diagnosis was emaciation; slight pitting edema of the extremities; acute hemorrhagic colitis, due to Bacillus dysenteriae, mannite-fermenting group; generalized caseous adhesive tuberculous peritonitis; scattered tubercles in the pleura, lungs, liver and spleen; acute caseous tuberculosis of the tracheobronchial, mesenteric and retroperitoneal lymph nodes; bilateral bronchopneumonia; infarction of the left kidney; marked fatty change of the liver; hyperplasia of the bone marrow of the skull; decubitus ulcer of the right buttock; degeneration of the peripheral nerves, nerve roots, spinal ganglia and cranial nerves; sclerosis of the posterior column of the spinal cord, and primary irritation of the large motor neurons.

Pathologic Changes in Nervous System.—Gross Appearance: Except for grayish discoloration of the posterior columns throughout the spinal cord, there was no conspicuous abnormality.

Microscopic Changes: Brain: The leptomeninges were thin and free from significant infiltration. The cytoarchitecture was in order. The nerve cells of the entire brain showed chromatolysis of various degrees but exhibited no distinct increase of lipoid in their cytoplasm. The nerve cells in lamina II tended to present a picture of shrinkage, while those in laminas III and V and the Purkinje cells showed fresh ischemic necrosis. The Betz cells were swollen and their central portions were chromatolytic, with the Nissl bodies displaced toward the periphery and the nucleus eccentrically situated (fig. 1). The glia cells remained unaffected. There was no infiltration, fatty degeneration or hyaline change of the pial or intracerebral blood vessels. The white substance was essentially normal.

Spinal cord: Changes similar to those in the Betz cells were noted in a few nerve cells in each anterior horn of the lumbar region. The gray substance was otherwise intact. The medullary sheaths of the posterior columns at this level were swollen and rarefied and showed formation of myelin balls. The axis-cylinders were equally involved. The scarlet red stain revealed lipoid globules, some of which were doubly refractile. Glial fibers were only slightly increased. The blood

vessels remained free. The changes in the posterior columns were uniformly distributed in a scattered fashion, with no predilection for the course of the blood vessels. The medullary sheaths elsewhere were somewhat swollen. In the thoracic region a similar sclerotic process was noted in the fasciculus gracilis, but it appeared to be denser and assumed a triangular shape, the area being symmetrically bisected by the posterior commissure, with the broad base lying immediately on the margin of the spinal cord (fig. 2). This sclerotic process extended up to the cervical region, where it spread laterad to involve a narrow strip of each fasciculus cuneatus. The Clarke columns, as well as the posterior and lateral horns, had not undergone conspicuous changes.

Nerve roots: The posterior nerve roots of the cauda equina showed proliferation of the endoneurium, perineurium and the cells of Schwann and infiltration with a few granular cells. There were no infiltrating hematogenic elements. The

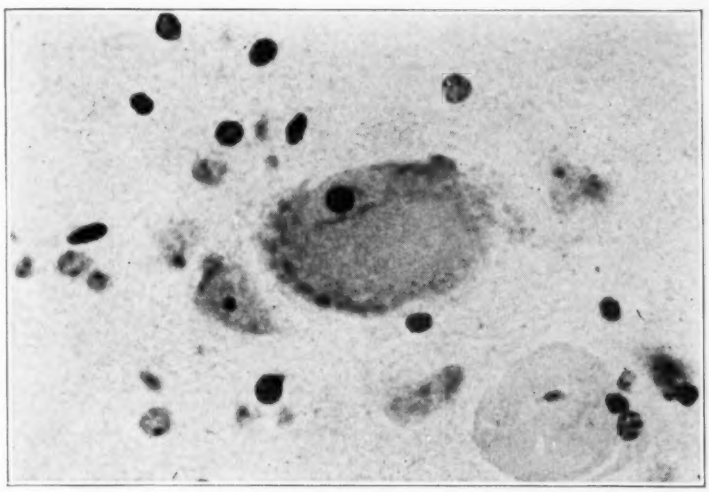

Fig. 1.—Primary irritation of the Betz cells. Nissl stain; × 343.

blood vessels were unaltered. The fine scaffolding of the medullary sheaths was indistinct. Instead, the sheaths were swollen, dark staining and transformed into isolated myelin balls and dustlike granules. The deeply stained myelin masses were distributed around the axis-cylinders and were directly connected with the delicate myelin-loaded outer zone. The axis-cylinders were reduced in number, exhibited fragmentation and distortion into spirals and presented isolated masses and *Effilochment*. Both free and engulfed lipoid substances were noted, some of which were doubly refractile. The distribution of these changes was independent of the blood vessels. The anterior nerve roots of the same region presented a similar picture, but one much milder than that of the posterior roots. The medullary sheaths had undergone only alteration of the fine meshwork and occasional swelling. The axis-cylinders showed occasionally bandlike swelling. There was, however, no definite formation of the dissolution products. At higher levels of the spinal cord the nerve roots were also affected, but relatively mildly as compared with the changes in the cauda equina.

Dorsal spinal ganglia: The ganglion cells were atrophic and showed a moderate increase of the lipoid pigment in the cytoplasm. Both the intraganglionic and the extraganglionic medullary sheaths were degenerated, with a little lipoid substance distributed along the course of the fibers.

Cranial and peripheral nerves: The optic nerve and chiasm and the auditory nerve roots were normal. There were a few isolated lipoid-containing granular cells in the root of the trigeminal nerve. The femoral, sciatic, median, ulnar and radial nerves on both sides were much more severely degenerated than the nerve roots. The process was of extreme severity in both sciatic nerves (fig. 3), fairly pronounced in the left ulnar nerve, moderately severe in the right femoral, right radial, right ulnar and left femoral nerves, the intensity being about equal to that of the posterior nerve roots of the cauda equina, and least noticeable in the left radial nerve. There was marked proliferation of the endoneurium, peri-

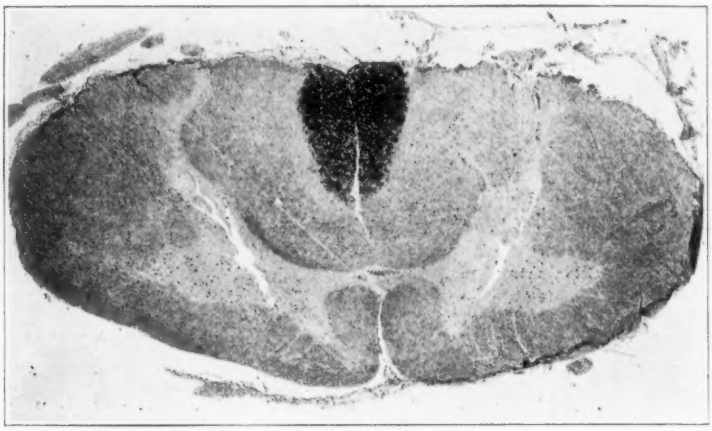

Fig. 2.—Lipoid granules in the fasciculus gracilis of the lower cervical segment. Marchi stain; × 7.

neurium and the cells of Schwann. The blood vessels were moderately thickened and showed a moderate increase of cellular elements in the wall but no infiltration.

Case 2.—A Chinese man aged 26 was admitted to the Red Cross base hospital because of diarrhea and an "intra-abdominal condition." The clinical impression was that of pulmonary tuberculosis and tuberculosis of the intestine and peritoneum with ascites. He died on Oct. 24, 1937.

Autopsy.—The pathologic diagnosis was emaciation, slight pitting edema of the feet, ascites, hydrothorax and hydroperitoneum; atrophy of the skeletal musculature and viscera; gelatinous degeneration of the bone marrow; extensive subacute diphtheritic and ulcerative colitis (B. dysenteriae [?]); subacute mesenteric and retroperitoneal lymphadenitis; hyalinization of the testicular tubules; slight bilateral lobular pneumonia; tuberculosis of the tracheobronchial lymph nodes; bilateral fibrous pleural adhesions; a small infarct of the hypophysis; degeneration of the nerve roots; sclerosis of the posterior columns of the cord, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: The brain appeared pale but otherwise normal. Cross sections of the spinal cord showed definite pallor of the fasciculus gracilis at the cervical level, the column becoming less distinct toward the caudal region.

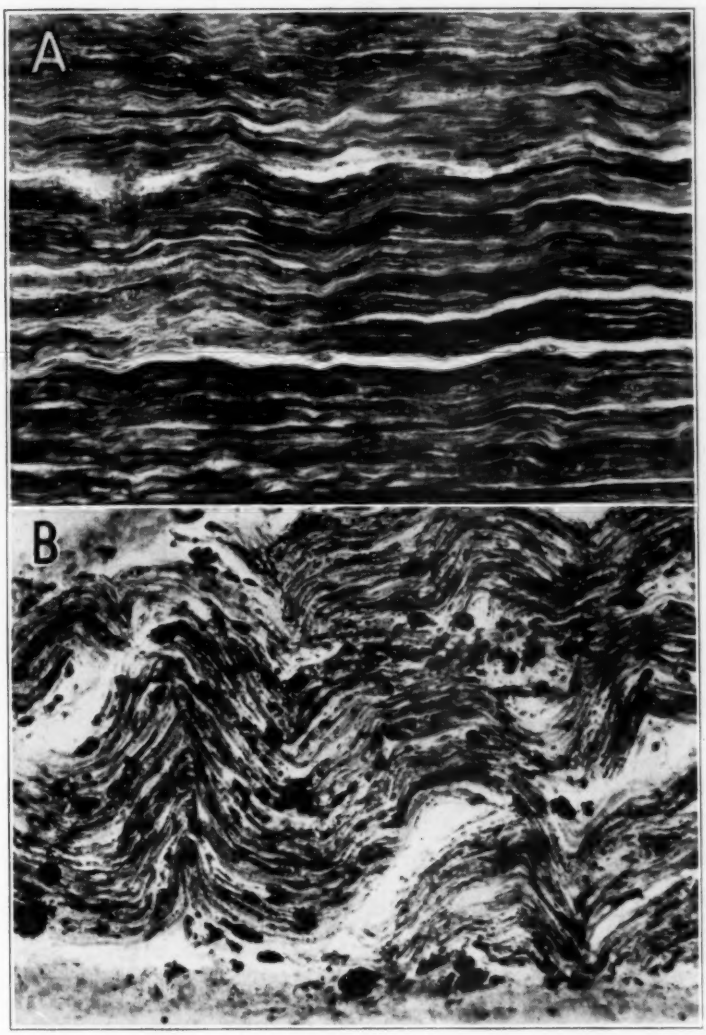

Fig. 3.—*A*, demyelination of the left sciatic nerve. Spielmeyer stain; × 155. *B*, lipoid granules in the left sciatic nerve. Scarlet red stain; × 155.

Microscopic Observations: Brain: In general, the changes in this case were comparable to those in case 1. Nevertheless, there were severe changes of the nerve cells in the cortex, basal ganglia and brain stem. Furthermore, the Betz cells showed not only primary irritation but severe disintegration. Primary irritation occurred also in the nucleus of the hypoglossal nerve.

Spinal cord: Some of the nerve cells in the anterior horns of the lumbar segments showed primary irritation. There was slight proliferation of the glia cells along the posterior commissure. The posterior columns presented a picture of sclerosis similar to that in case 1. The dorsomedial field on each side of the posterior commissure was particularly involved. This sclerotic process was continuous with that at upper levels. In the thoracic region it involved symmetrically the whole field of the posterior columns, while in the cervical segments it became triangular over the dorsomedial portion and covered also a part of each fasciculus cuneatus, to a more intense degree than was observed in case 1.

Nerve roots of the cauda equina: The posterior nerve roots exhibited changes similar to those in case 1 but to a more intense degree (fig. 4). The anterior

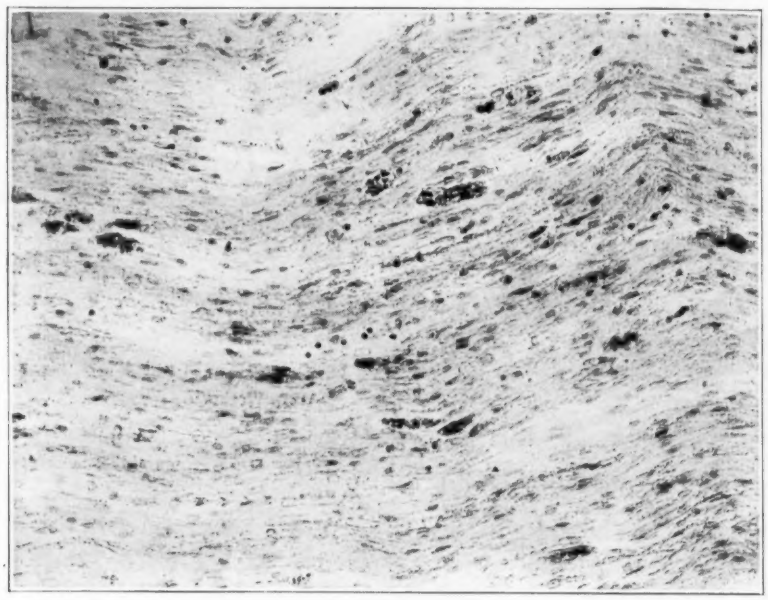

Fig. 4.—Lipoid granules in the posterior nerve root at the cauda equina. Scarlet red stain; × 172.

nerve roots, unlike those in case 1, show deposition of lipoid granules in the perineurial tissue.

Case 3.—A man aged 40 had diarrhea, probably due to bacillary dysentery. He died on Oct. 17, 1937.

Autopsy.—The general pathologic changes were emaciation; nutritional edema; acute ulcerative ileocolitis; bilateral lobular pneumonia with localized bronchiectasis of the lower lobe of the left lung; acute fibrinous pleuritis; chronic caseous tuberculosis of the apex of the left lung with pleural fibrous adhesions; fatty change of the liver; scar of the spleen; peritoneal fibrous adhesions; moderate colloid goiter; accessory spleen; degeneration of the nerve roots; sclerosis of the posterior columns of the cord, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: The changes in the brain and the spinal cord appeared similar to those in case 1.

Microscopic Observations: Brain: The leptomeninges were slightly thickened but not infiltrated. The surface and deep blood vessels were congested, and the latter showed in Nissl preparations frequent depositions of greenish yellow pigment in the perivascular spaces. There was no evidence of arteriosclerosis. Some of the pacchionian bodies were calcified. A few Betz cells and the nerve cells in the nucleus of the hypoglossal nerve showed primary irritation. Other nerve cells were either chromatolytic or shrunken. The glia cells remained unaffected.

Spinal cord: The meninges were essentially normal. A few of the nerve cells in the lateral groups of the anterior horns and in the lateral horns of the lower

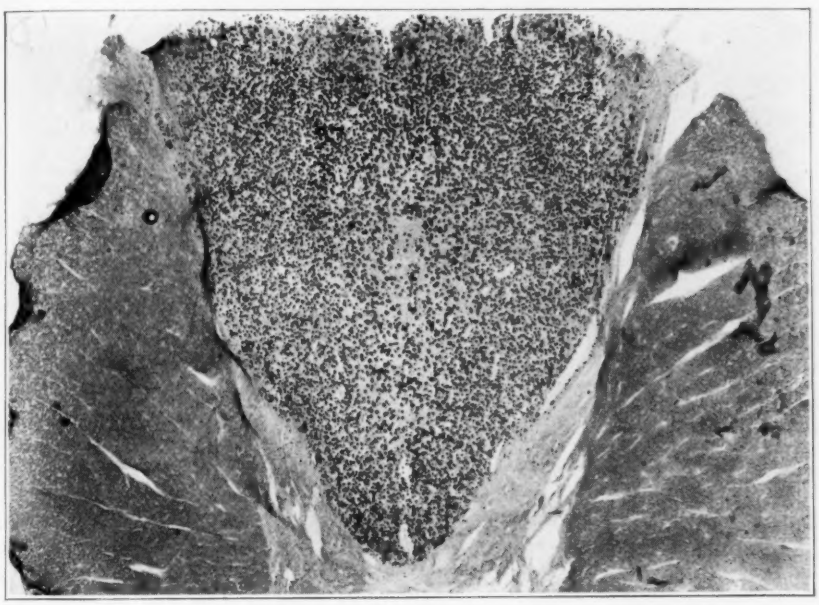

Fig. 5.—Lipoid granules in the posterior columns of the thoracic segment. Scarlet red stain; × 16.5.

cervical region showed primary irritation. The posterior columns appeared to be spongy and presented moderate proliferation of glia, with formation of characteristic gitter and gemästete cells. The medullary sheaths and the axis-cylinders of the entire posterior columns had undergone a pronounced degree of degeneration, accompanied by a rich deposition of lipoid substance (fig. 5) and a definite increase of the glial fibers. This sclerotic process was distinctly more complete in the fasciculus gracilis than in the fasciculus cuneatus. Similar, but less marked, changes of the posterior columns were noted at the upper and the lower level of the spinal cord (fig. 6).

Nerve roots of the cauda equina: The posterior nerve roots assumed the same picture as that in case 2 (fig. 7 *A* and *B*), while the anterior nerve roots were not unlike those in case 1.

Case 4.—A man aged 28 was admitted to the Red Cross base hospital on Sept. 5, 1937 with a history of hemoptysis, night sweats, fever and cough, signs of pulmonary tuberculosis on the left side and diarrhea. He died on October 30.

Autopsy.—The general pathologic observations were emaciation; edema of the extremities, ascites and hydrothorax; brown atrophy of the heart and liver; gelatinous degeneration of the bone marrow; tuberculous ulcers of the trachea, larynx, pharynx, ileum, cecum and ascending colon; bilateral acute caseous pulmonary tuberculosis with cavity formation and dense fibrous pleural adhesions on the left side; acute caseous tuberculosis of the tonsils, tracheobronchial and

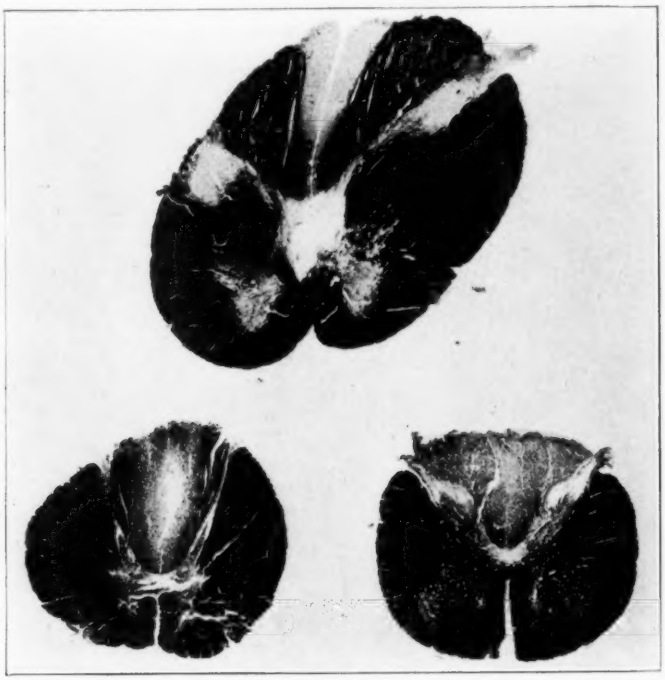

Fig. 6.—Demyelination of the posterior columns of the cervical, thoracic and lumbar segments. Schroeder's stain; × 6.

mesenteric lymph nodes and liver; slight lobular pneumonia; a negative Kline reaction; degeneration of the nerve roots; sclerosis of the posterior columns of the spinal cord, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: The brain was pale and the ventricular system somewhat dilated. The posterior columns of the spinal cord were grayish.

Microscopic Observations: Brain: The leptomeninges were occasionally infiltrated with small round cells but were of normal thickness. The changes in the nerve cells were diffuse and varied from chromatolysis and shrinkage to ischemic necrosis and severe disintegration. Furthermore, the changes in the Betz cells and the nerve cells in the oculomotor nucleus were suggestive of primary irritation.

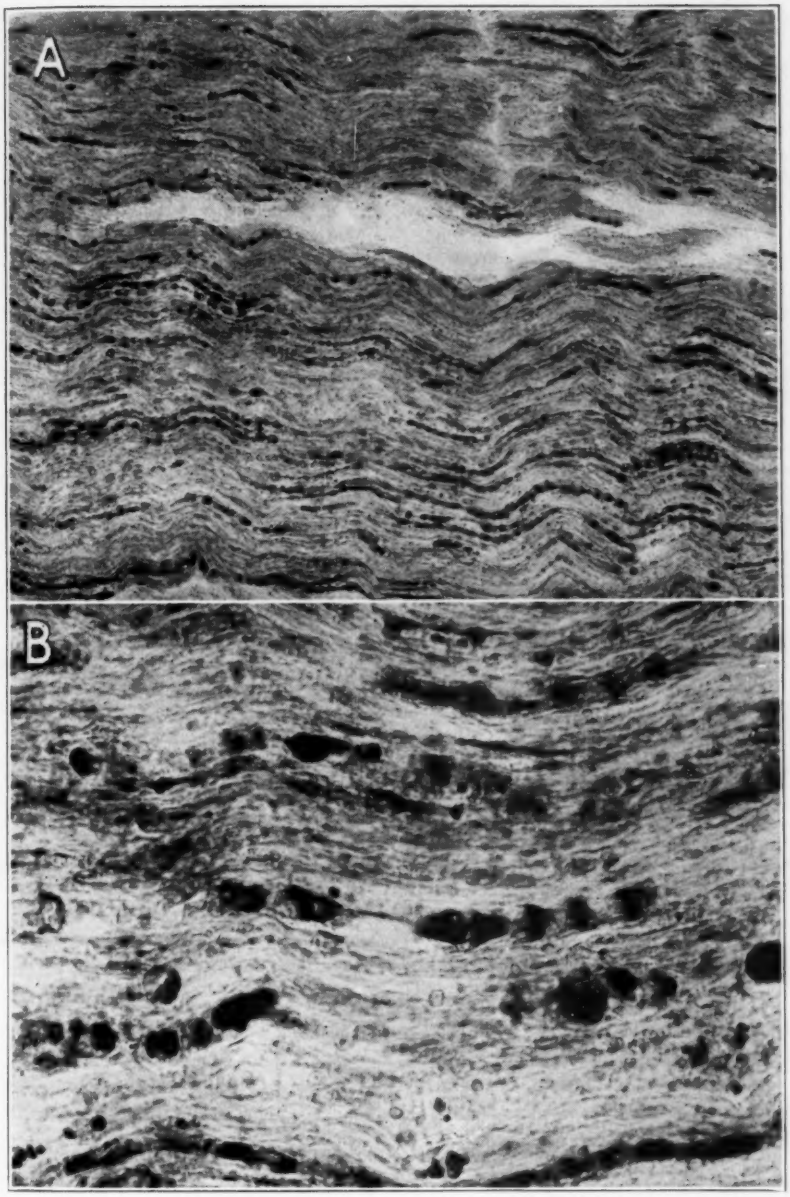

Fig. 7.—*A*, demyelination of the posterior nerve root at the cauda equina. Spielmeyer stain; × 106.

B, demyelination of the posterior nerve root at the cauda equina. Spielmeyer stain; × 410.

The glia was not involved. The deep blood vessels showed deposition of greenish pigment around their walls similar to that in case 3. The blood vessels themselves, however, were free from infiltration and organic alteration.

Spinal cord: The leptomeninges were normal. The intramedullary blood vessels were engorged. The nerve cells in the anterior horns at all levels showed vacuolation of the cytoplasm, and most of them were shrunken. The nerve cells in the lateral horns of the thoracic segments exhibited primary irritation. There was a slight but definite increase of the glia cells along the posterior commissure in the cervical and thoracic regions. In Spielmeyer preparations one could see irregular light-staining patches with swelling of the sheaths distributed throughout the posterior columns in the thoracic segments and irregularly scattered in the

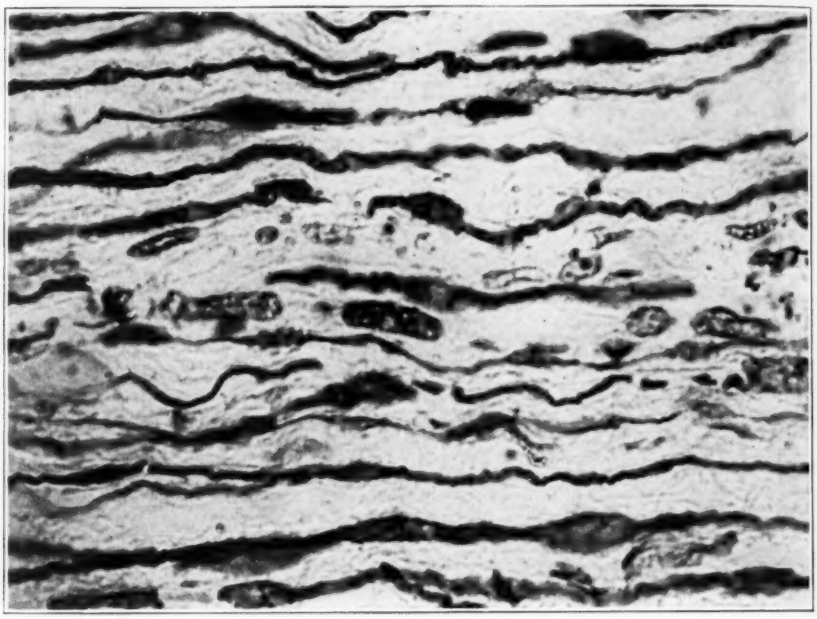

Fig. 8.—Swelling, distortion and fragmentation of the axis-cylinders of the posterior nerve root at the cauda equina. Bielschowsky stain; × 667.

cervical segments, with none in the lumbar segments. There was nowhere an increase of the glial fibers.

Nerve roots of the cauda equina: Both the anterior and the posterior nerve roots showed changes similar to, but less marked than, those in case 1 (fig. 8).

CASE 5.—A man aged 35 was admitted to the Red Cross base hospital on Sept. 22, 1937. The clinical impression was that of dysentery, bronchitis (?) and pulmonary tuberculosis (?). He died on November 18.

Autopsy.—The general pathologic observations were emaciation; atrophy of the skeletal musculature, liver, heart, thyroid and testicular tubules; secondary anemia; hyperplasia and gelatinous degeneration of the bone marrow; chronic and acute ulcerative diphtheritic colitis (B. dysenteriae [?]); tuberculous ulcers

of the ileum; chronic caseous tuberculosis of both lungs, with cavity formation in the upper lobes; bilateral pleural fibrous adhesions; slight hydrothorax; tuberculosis of the pericolic and omental lymph nodes; peritoneal fibrous adhesions; healed infarct of the spleen (?); decubitus ulcer of the trochanteric region; degeneration of the peripheral nerves and the posterior nerve roots; sclerosis of the posterior columns of the spinal cord, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: Except for pallor of the brain and the posterior columns of the spinal cord, there was no macroscopic abnormality.

Microscopic Observations: Brain: The covering membranes were normal. The intracerebral blood vessels were engorged and greenish granules were accumulated in the Virchow-Robin spaces. There was no evidence of inflammation or regressive changes of the vascular apparatus. The pattern of the cellular structures was undisturbed. Many nerve cells had dropped out; many were chromatolytic or shrunken and many showed severe types of changes. Furthermore, the Betz cells exhibited a typical picture of primary irritation, and the Purkinje cells had undergone homogeneous degeneration. The glia cells in the white substance tended to arrange themselves in irregular patches, but no characteristic form could be observed.

Spinal cord: The covering membranes were intact. The nerve cells of the anterior horns were in general chromatolytic or shrunken, and those in the cervical segments were suggestive of primary irritation. The glia cells in the posterior columns, especially along the commissure, were proliferated and took the form of rod cells, gitter cells and large naked, vesicular nuclei in the Nissl picture. Some of the blood vessels in the posterior columns occasionally showed infiltration with a few small round cells. Special stains for myelin sheaths, axis-cylinders and dissolution products revealed extensive degeneration of the nerve fibers, with but slight organization throughout the posterior columns at all levels (fig. 9). Lipoid granules were also noted in one of the posterior horns of the thoracic portion of the cord. The intensity of the process was much greater in the thoracic and lumbar than in the cervical segments and was more distinct in the fasciculus gracilis than in the fasciculus cuneatus.

Nerve roots of the cauda equina: The posterior nerve roots showed changes similar in nature and intensity to those in case 2. The anterior nerve roots were essentially normal.

Peripheral nerves: The peripheral nerves had undergone more pronounced degeneration than the roots.

CASE 6.—A Chinese man aged 34 was admitted to the Red Cross base hospital because of feverishness and occasional attacks of diarrhea for two months. The clinical impression was that of far advanced pulmonary tuberculosis. He died on Jan. 19, 1938.

Autopsy.—The general pathologic diagnosis was emaciation; acute and chronic caseous pulmonary tuberculosis with multiple bilateral cavity formation; acute fibrinopurulent pleuritis with effusion on the right side; acute fibrinous pleuritis with atelectasis of the left lung; bilateral fibrous pleural adhesions; tuberculosis of the tracheobronchial, mediastinal and cervical lymph nodes; tuberculous ulcerative ileocolitis; tuberculosis of the mesenteric, pericolic and retroperitoneal lymph nodes; disseminated tubercules in the spleen and liver; kala azar; moderate splenomegaly; hyperplasia and gelatinous degeneration of the bone marrow; central atrophy of

the liver; moderate ascites and hydropericardium; scarring of the kidneys; ulcers of the esophagus and rectum; decubitus ulcer of the coccygeal region; degeneration of the peripheral nerves, spinal ganglia and posterior nerve roots; sclerosis of the posterior columns; marginal degeneration (Marchi) of the spinal cord and primary irritation of the Betz cells.

Pathologic Changes in the Nervous System.—Gross Appearance: The brain and the posterior columns of the spinal cord were pale, but were otherwise normal.

Microscopic Observations: Brain: There were areas of slight lymphocytic infiltration in the leptomeninges. The perivascular spaces, particularly in the deeper white substance, were dilated and showed accumulation of greenish pigments,

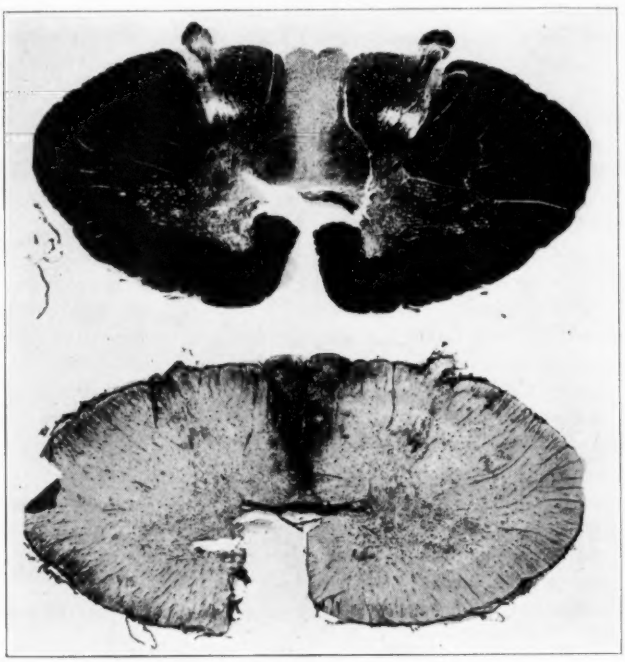

Fig. 9.—Upper: demyelination of the posterior columns of the cervical segment. Schroeder stain; × 8.

Lower: sclerosis of the fasciculus gracilis of the cervical segment. Holzer stain; × 8.

accompanied by a slight increase in the glia cells. There were foci of devastation in the cerebral cortex. The cortical nerve cells showed noncharacteristic changes of various degrees of intensity. The large pyramidal cells, especially the Betz cells, presented a typical picture of primary irritation. However, the cytoarchitecture remained unaffected.

Spinal cord: Some of the anterior horn cells were chromatolytic and vacuolated, but not altered as in primary irritation. In the fasciculus gracilis in the cervical region the glia cells were considerably proliferated and had already been transformed into gemästete and gitter cells. Marchi degeneration was noted in

the margin and in the posterior columns. Stains for neutral fat and myelin sheaths revealed a pronounced process of degeneration in the fasciculus gracilis, particularly at the cervical level.

Spinal nerve roots: The posterior nerve roots of the cauda equina were degenerated, as revealed by the scarlet red stain, while the anterior nerve roots at the same level were only slightly involved. The cervical posterior nerve roots presented a picture similar to that of the anterior roots and were free from dissolution products.

Dorsal spinal ganglia: Moderately advanced degeneration of the nerve fibers was noted in the peripheral nerves and appeared to be more pronounced in the lower than in the upper extremities.

CASE 7.—A man aged 25 was admitted to the Red Cross base hospital on Sept. 6, 1937 because of feverishness and frequent stools of four months' duration. The clinical diagnosis was chronic dysentery and anemia. He died on Jan. 26, 1938.

Autopsy.—The general pathologic diagnosis was emaciation; bacillary dysentery (with a negative culture); chronic and acute ulcerative ileocolitis; subacute and acute caseous tuberculosis of the lungs, pleurae and tracheobronchial lymph nodes; bilateral lobular pneumonia and acute fibrinopurulent pleuritis with pleural effusion; tubular degeneration of the kidneys; fatty change and atrophy of the liver; ascites and edema of the hands and feet; hyperplasia and gelatinous degeneration of the bone marrow of the femur; Meckel's diverticulum; degeneration of the peripheral nerves, spinal dorsal ganglia and posterior nerve roots; sclerosis of the posterior colums of the spinal cord; marginal degeneration (Marchi) of the spinal cord, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Microscopic Observations: Brain: The mesenchymal tissue and the glia were normal. The cytoarchitecture remained in order. There were small pale areas in the cerebral cortex. The nerve cells showed various types of changes, ranging from simple chromatolysis and shrinkage to ischemic necrosis. Some of the Betz cells presented a picture of primary irritation. There was no increase of the pigments.

Spinal cord: The anterior horn cells were slightly chromatolytic, and a few of those at the cervical level showed a picture similar to that of the Betz cells. The margin of the posterior columns gave a positive Marchi reaction. Stains for neutral fat and myelin sheaths revealed degeneration of the fasciculus gracilis, which was apparently more conspicuous at the cervical than at lower levels.

Spinal nerve roots: The posterior nerve roots of the cauda equina were moderately degenerated, while the anterior nerve roots at the same level showed occasional fat granules in the interstitial tissue only. The changes in the cervical posterior nerve roots resembled those in the anterior nerve roots of the cauda. The cervical anterior and the thoracic anterior and posterior nerve roots were free from products of dissolution.

Dorsal spinal ganglia: The nerve cells were either atrophic or swollen and chromatolytic, with the nuclei displaced peripherally.

Peripheral nerves: The peripheral nerves of the lower extremities were more profoundly affected than those of the upper extremities. The Marchi method gave the same picture as that revealed by the scarlet red stain.

CASE 8.—A Chinese man aged 21 was admitted to the Red Cross base hospital on Sept. 3, 1937 because of fever, night sweats and impaired appetite of five months' duration. There were signs of malnutrition and empyema on the left side

of the chest, moderate diarrhea and splenomegaly. The Wassermann reaction of the blood was negative. There were no malaria parasites or Leishmania Donovi bodies. The reaction for globulin was 1 plus. There was no leukocytosis and no anemia. The patient died on December 14.

Autopsy.—The general pathologic observations were emaciation; edema of the scrotum and lower extremities; tuberculous ulceration of the intestine; fibrous and caseous tuberculous pleuritis on the left side; tuberculous pericarditis; left pleural effusion; atelectasis in the left lung; acute caseous miliary tuberculosis of the femur and vertebrae; acute caseous tuberculosis of the cervical, anterior mediastinal, tracheobronchial, mesenteric and retroperitoneal lymph nodes; papillary adenoma of the thyroid; decubitus ulcer of the left buttock; ankylostomiasis; mild degeneration of the peripheral nerves and posterior nerve roots; mild sclerosis of the posterior columns of the spinal cord, and suggestive primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: There was no macroscopic alteration.

Microscopic Observations: Brain: Fresh red blood cells were noted in the subarachnoid spaces. The surface and deep blood vessels were hyperemic. The nerve cells were diffusely chromatolytic, and there were foci of devastation in the cornu ammonis. Some of the Betz cells were suggestive of primary irritation.

Spinal cord: Except for a few fresh red blood cells in the leptomeninges and signs of primary irritation in some of the nerve cells of the anterior horns in the lumbar region, Nissl preparations revealed no conspicuous change. Special stains for the ingredients of the nerve fibers and the dissolution products showed only a few isolated lipoid globules in the white substance along the posterior commissure, which were relatively more pronounced in the lower than in the upper segments.

Nerve roots of the cauda equina: The changes of the posterior nerve roots were similar to those of the anterior nerve roots in case 2. The anterior roots were normal.

Peripheral nerves: Scattered patches of lipoid substances were present and appeared to be somewhat more extensive than in the nerve roots.

Case 9.—A man aged 20 was admitted to the Red Cross base hospital with high fever, clinical evidence of consolidation of the upper portion of the left lung, with pleural thickening and effusion, resistant abdomen and diarrhea. The clinical impression was that of acute pulmonary tuberculosis, tuberculous pleurisy with effusion on the left side and tuberculosis of the intestine and peritoneum. He died on Jan. 6, 1938.

Autopsy.—The general pathologic observations were emaciation; extensive bilateral subacute caseous pulmonary tuberculosis (bronchiogenic); caseous tuberculous pleurisy on the left side; caseous tuberculosis of the tracheobronchial, mediastinal and cervical lymph nodes; extensive tuberculous ulcerative enterocolitis; acute caseous tuberculosis of the mesenteric, pancreatic, pericecal, perigastric and retroperitoneal lymph nodes; generalized caseous tuberculous peritonitis; caseous tuberculosis of the prostate gland, verumontanum and right seminal vesicle; disseminated tubercles in the spleen, liver and bone marrow; lobular pneumonia; secondary anemia; hyperplasia of the bone marrow; marked fatty change of the liver; atrophy of the thyroid; fibrous pleural and peritoneal adhesions; healed adhesive periappendicitis; mild degeneration of the peripheral nerves, dorsal spinal

ganglia and spinal posterior nerve roots; Marchi degeneration of the margin and the posterior columns of the spinal cord; primary irritation of the nerve cells in the lateral horns of the spinal cord, and premature arteriosclerosis.

Pathologic Changes in the Nervous System.—Gross Appearance: No significant alteration was noted.

Microscopic Observations: Brain: The leptomeninges were distended with fluid and contained foci of hemolyzed red blood cells but were not thickened and not significantly infiltrated. The cytoarchitecture remained undisturbed. Both the ganglion and the glia cells appeared to be essentially normal. In the deeper white substance in the glia cells tended to accumulate around the blood vessels. Both the surface and the deep blood vessels were congested, with the endothelium somewhat swollen and the cells on the wall slightly proliferated. The perivascular spaces were moderately dilated.

Spinal cord: The ganglion cells of the lateral horns in the thoracic segments showed primary irritation. The margin and the posterior columns gave a positive reaction in Marchi preparations. The scarlet red and Spielmeyer technics revealed nothing significant.

Spinal nerve roots: There were a few small foci of products of fat dissolution in the posterior nerve roots in the cervical and lumbar regions. The anterior nerve roots appeared normal even in Marchi-stained sections.

Dorsal spinal ganglia: Besides diminution in number, the ganglion cells were atrophic and showed vacuolation. The capsular cells were not definitely increased.

Peripheral nerves: An extensive Marchi reaction was noted. The scarlet red and Spielmeyer technics revealed a slightly more advanced process than in the posterior nerve roots.

Case 10.—A Chinese man aged 28 was admitted to the Red Cross base hospital on Oct. 20, 1937 with a history of having had a cough for one year and swelling of the face and legs for one week. The clinical impression was that of far advanced pulmonary tuberculosis and nutritional edema. He died on Jan. 15, 1938.

Autopsy.—The general pathologic observations were emaciation; chronic and acute tuberculosis of the lungs with multiple cavity formation; tuberculosis of the pleura on the left side and the tracheobronchial lymph nodes; fibrous pleural adhesions on the left side; tubercles in the ileum; tubular degeneration of the kidneys; edema of the subcutaneous and retroperitoneal tissue; pleural and pericardial effusion; atrophy of the liver; gelatinous degeneration of the bone marrow of the femur; degeneration of the peripheral nerves, dorsal spinal ganglia and nerve roots; Marchi degeneration of the spinal cord; primary irritation of the large motor nerve cells, and premature arteriosclerosis.

Pathologic Changes in the Nervous System.—Gross Appearance: Except for hyperemia of the brain and paleness of the posterior columns of the spinal cord, no change was evident to the naked eye.

Microscopic Observations: Brain: There were a few small areas of lymphocytic infiltration in the leptomeninges. Some of the small blood vessels in the superficial layers of the cortex showed hypertrophy of the endothelial cells, and those in the deeper white substance exhibited slight accumulation of the greenish pigments and mild proliferation of the glia cells in their perivascular spaces. The ganglion cells were either diffusely chromatolytic or severely altered, with incrustations and satellitosis. The Betz cells had undergone primary irritation. The cytoarchitecture was, however, in order.

Spinal cord: The ganglion cells in the anterior horns, especially in the lumbar region, showed either primary irritation or vacuolation of the cytoplasm. Staining by Marchi's method revealed diffuse degeneration of the fiber tracts, the margin and the posterior columns being more involved.

Spinal nerve roots: The posterior nerve roots of the cauda equina presented scattered foci of dissolution products, while the corresponding anterior nerve roots gave a positive reaction to the Marchi stain only. The cervical posterior nerve roots were much less severely affected than those of the cauda equina. The cervical anterior and the thoracic anterior and posterior nerve roots gave a positive reaction in Marchi preparations only.

Dorsal spinal ganglia: The ganglion cells were somewhat swollen or atrophic, the capsular cells being preserved.

Peripheral nerves: The peripheral nerves of the extremities were definitely damaged, and the process of degeneration appeared to be much more intensive than that of the nerve roots.

CASE 11.—A man aged 24 was admitted to the Red Cross base hospital on Sept. 3, 1937 because of diarrhea and severe cough and signs of malnutrition, anemia and pulmonary tuberculosis. He died on October 24.

Autopsy.—The general pathologic observations were emaciation, slight pitting edema of the hands and feet; ulcers of the intestine; caseous pulmonary tuberculosis of the lower lobe of the right lung; caseous tuberculous pleuritis with adhesions on the right side; tuberculosis of the tracheobronchial lymph nodes; bilateral bronchopneumonia; hemosiderosis of the spleen and bone marrow of the femur; chronic perihepatitis; ankylostomiasis; mild degeneration of the posterior nerve roots, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: Macroscopic examination of the brain and spinal cord yielded normal results.

Microscopic Observations: Brain: The covering membranes were normal. The surface and deep blood vessels were congested, and the latter showed perivascular accumulation of the greenish granules. The nerve cells showed diffuse nonspecific changes. Besides, one could note severe disintegration of the large pyramidal cells, ischemic necrosis of Sommer's sector, homogeneous degeneration of the Purkinje cells and primary irritation of the Betz cells and the nerve cells in the nuclei of the oculomotor (fig. 10), the trochlear and hypoglossal nerves. The cellular pattern, however, was in order, and the interstitial tissue remained unchanged.

Spinal cord: Aside from fresh perivascular hemorrhages in the anterior and posterior horns of the cervical portions of the cord, there was primary irritation of some of the nerve cells of the anterior horns in the lumbar region.

Nerve roots of the cauda equina: The picture was similar to that noted in case 8.

CASE 12.—A Chinese man aged 32 was admitted with a history of having had a cough with hemoptysis for one year and frequent bloody stools for one month. There were signs of pulmonary tuberculosis in the upper lobe of the right lung and of malnutrition. He died on Dec. 13, 1937.

Autopsy.—The generalized pathologic observations were emaciation; gelatinous degeneration of the bone marrow of the femur; extensive tuberculous ulcers of the small and large intestine; chronic and acute caseous tuberculosis of the lungs with cavity formation in the upper lobe of the right lung; tuberculosis of the

tracheobronchial and mesenteric lymph nodes; scattered tubercles in the liver and spleen; ascites; mild degeneration of the posterior nerve roots, and primary irritation of the large motor nerve cells.

Pathologic Changes in the Nervous System.—Gross Appearance: Examination of the brain and spinal cord with the naked eye revealed nothing pathologic.

Microscopic Observations: Brain: The leptomeninges were infiltrated in places with a few small round cells. The blood vessels were essentially normal except for clumps of greenish pigment around the deeper ones. All the nerve cells showed chromatolysis and shrinkage. Furthermore, the Betz cells had undergone a typical change of primary irritation and the Purkinje cells homogeneous degeneration. The glia cells did not show deviations.

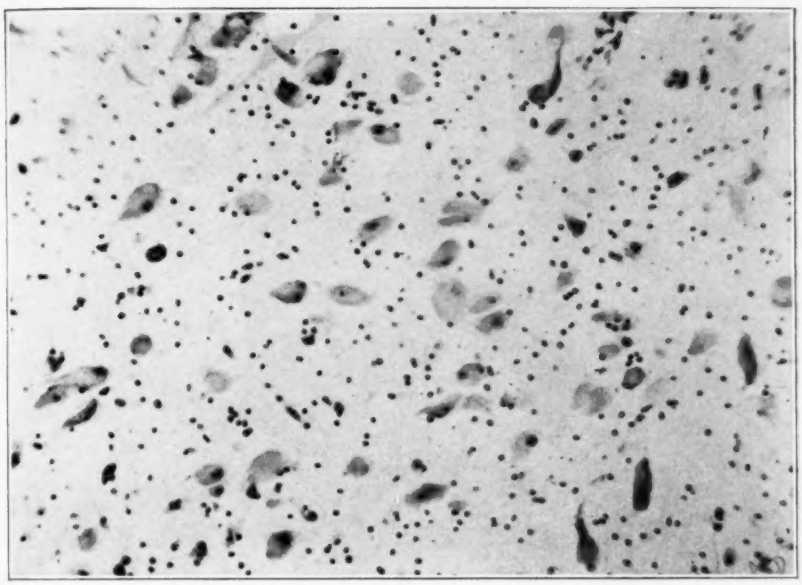

Fig. 10.—Primary irritation of the nerve cells in the oculomotor nucleus. Nissl stain; × 98.

Spinal cord: Chromatolysis of the anterior horn cells was the only significant change.

Nerve roots of the cauda equina: The lesion was similar to, but even milder than, that in case 8.

Case 13.—A man aged 28 was admitted to the Red Cross base hospital on Sept. 23, 1937 because of hemoptysis for three weeks, watery stools with mucus, negative for tubercle bacilli and parasites, and irregular fluctuations of temperature. The clinical impression was that of tuberculosis of the lungs and intestine, chronic dysentery and pellagra. He died on Jan. 5, 1938.

Autopsy.—The general pathologic observations were symmetric hyperpigmentation and hyperkeratosis of the backs of both hands (fig. 11); chronic acute ulcerative colitis, with formation of mucous cysts; marked emaciation; atrophy

of the internal organs (liver, heart, spleen and tongue); early periportal cirrhosis of the liver; ascites; moderate edema of the legs; bilateral lobular pneumonia; bilateral fibrous pleural adhesions; siderosis of the spleen; degeneration of the peripheral nerves, dorsal spinal ganglia and spinal nerve roots; Marchi changes in the posterior columns, spinocerebellar and pyramidal tracts; diffuse fatty degeneration of the ganglion cells; primary irritation of the large motor nerve cells, and premature arteriosclerosis.

Pathologic Changes in the Nervous System.—Gross Appearance: The brain was pale and atrophic. The fasciculus gracilis and lateral tracts on the right side of the cervical portion of the spinal cord appeared grayish. No other change was apparent to the naked eye.

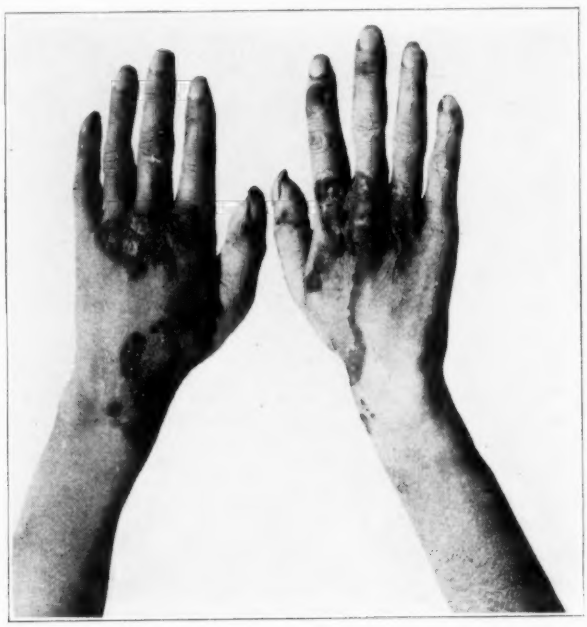

Fig. 11.—Symmetric hyperpigmentation and hyperkeratosis of the back of the hand.

Microscopic Observations: Brain: The leptomeninges of the frontal lobe were slightly hyperplastic and occasionally infiltrated with small round cells. There were a considerable number of melanophores in the covering membranes of the mesencephalon. The blood vessels in the pia as well as in the parenchyma exhibited moderate fibrosis, with occasional increase of the cellular elements. The perivascular spaces as a whole were dilated and showed accumulation of the glia cells and lipoid substances, especially in the deeper white substance. There was a marked degree of falling out of the cortical nerve cells, so much so that a normal cytoarchitectonic structure could hardly be made out with lower magnifications. Besides a general increase in the lipoid pigments, the nerve cells showed diffuse changes, ranging from slight tigrolysis and shrinkage to severe disintegration and mere shadows. Furthermore, one could note primary irritation of the

Betz cells and the nerve cells of the nucleus trochlearis, the pontile nuclei, the olives, the dorsal nucleus of the vagus and the nucleus of the hypoglossus nerve and of the thalamus and the subthalamicum. The glia cells were slightly

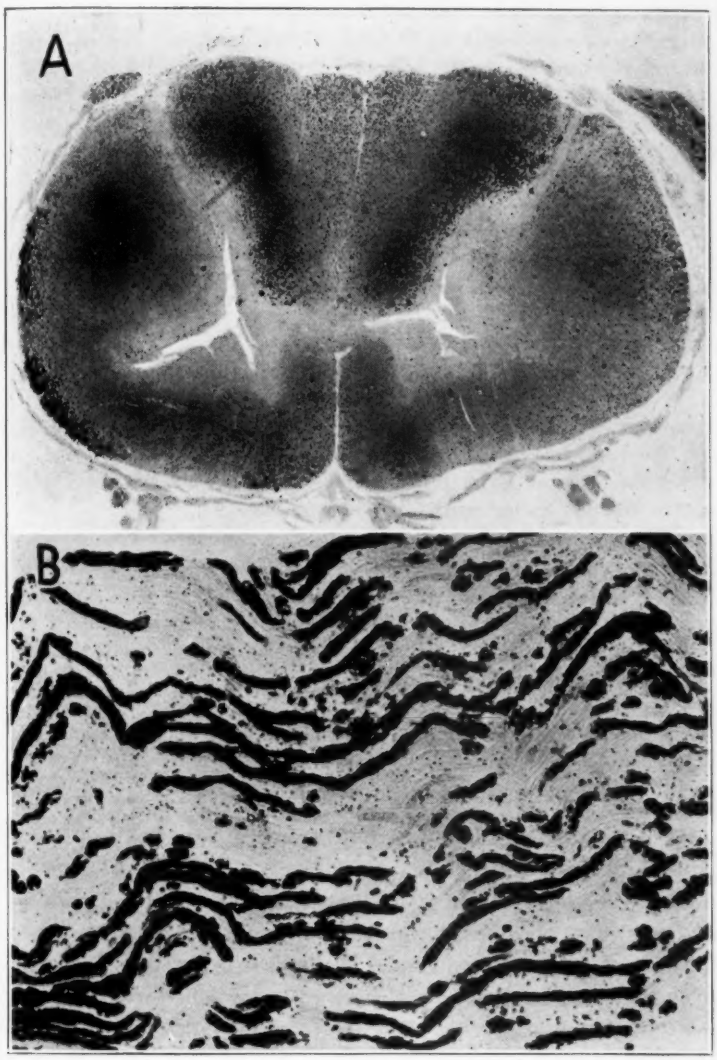

Fig. 12.—*A*, Marchi degeneration of the spinal funiculi and the nerve roots of the cervical segment. Marchi stain; × 8.

B, Marchi degeneration of the right ulnar nerve; × 155.

proliferated and were often arranged in clumps, but the Nissl picture presented no characteristic form. Small foci of fresh hemorrhages were observed in the floor of the fourth ventricle near the tractus solitarius.

Spinal cord: The nerve cells on the whole had undergone tigrolysis and were rich in pigment; atrophy and primary irritation of the cells of the anterior and posterior horns of the cervical and lumbar portions of the cord and of the lateral horns of the thoracic segment stood out prominently. Some of the anterior horn cells of the cervical region also had undergone vacuolation of their cytoplasm. The glia cells were somewhat proliferated. There was slight fibrosis of the blood vessels and the meninges. The Marchi technic gave a positive reaction, which was symmetrically distributed in the cord and in the nerve roots. The process involved the entire posterior columns, the lateral and anterior lateral tracts immediately ventral to the anterior horns and the posterior and anterior nerve roots. The degeneration was distinctly heavier along the medial border of each posterior horn and in the pyramidal and spinocerebellar tracts on one side than in the other regions (fig. 12 *A*). The involvement of the posterior nerve roots was much more pronounced than that of the anterior. The scarlet red stain showed occasional deposition of the lipoid globules in the perivascular spaces of the white substance, particularly along the posterior commissure. Stain for medullary sheaths with Spielmeyer's technic revealed a picture more or less the reverse of that with the Marchi technic.

Spinal nerve roots: There were numerous lipoid globules in the posterior spinal nerve roots, being most abundant at the cauda, less at the cervical level and least at the thoracic level. On the contrary, the anterior nerve roots, the optic nerve and the roots of the trigeminal, abducens, facial and auditory nerves gave a negative reaction in the scarlet red preparations.

Dorsal spinal ganglia: The ganglion cells were atrophic and pigmented.

Peripheral nerves: The interstitial cells were moderately proliferated. The small blood vessels showed tremendous thickening of the walls, increase of the cellular elements and hypertrophy of the endothelium, which often led to partial obliteration of the lumen. There was, however, no perivascular infiltration. The Marchi technic revealed no extensive reaction (fig. 12 *B*), while the scarlet red stain showed only isolated collections of neutral fat. These changes were more pronounced in the nerves of the lower extremities than in those of the upper.

SUMMARY OF THE CLINICOPATHOLOGIC CHANGES

Diarrhea, tuberculosis and malnutrition were the outstanding clinical features common to all these cases. However, a review of the foregoing protocols will convince one that the clinical observations made at the Red Cross base hospital, especially in connection with the neuropsychiatric status, were unusually scanty. In view of this, it is inconceivable that only in case 1 was there neurologic disturbance. Likewise, manifestations of a psychic disorder may well have been overlooked. Pellagrous cutaneous lesions were observed in case 13 only.

Distinct lesions of the intestine were observed in all the cases. There were 4 cases of bacillary dysentery, definite (case 1) or suggested (cases 2, 5 and 7); 8 cases of tuberculosis, definite (cases 4, 5, 6, 8, 9, 10 and 12) or suggested (case 11), and 2 cases of nonspecific colitis (cases 3 and 13).

Active tuberculosis of one or more organs was shown in all but case 13. In 4 cases the disease was disseminated (cases 1, 6, 8 and 9); in 11 cases it involved the lungs (cases 1, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12), and in 11 cases the lymph nodes, tracheobronchial (cases 1, 2, 4, 6, 7, 8, 9, 10, 11 and 12), mesenteric (cases 1, 4, 5, 6, 8, 9 and 12) or retroperitoneal (cases 1, 6, 8 and 9), and in 6 cases the serous cavities, the pleural (cases 1, 7, 8, 9, 10 and 11), the peritoneal (cases 1, 8 and 9) or the pericardial (case 8).

Emaciation and atrophy of the internal organs were noted in all cases. Nutritional edema of the extremities was noted in 9 instances (cases 1, 2, 3, 4, 7, 8, 10, 11 and 13). Excessive fluid in one or more serous cavities was demonstrated in 9 cases: ascites (cases 2, 4, 6, 7, 10, 12 and 13); hydrothorax (cases 2, 4, 5, 6, 7, 8 and 10), and hydropericardium (cases 2, 6 and 10). Adhesions of the serous cavities were observed in 11 cases: pleural (cases 2, 3, 4, 5, 6, 8, 9, 10, 11 and 13) and peritoneal (cases 1, 3, 5 and 9).

Other general pathologic conditions had the following distribution:

	Case No.	No of Cases
Gelatinous degeneration of the bone marrow	2, 4, 5, 6, 7, 10, 12	7
Hyperplasia of the bone marrow	1, 5, 6, 7, 9	5
Fatty degeneration or central atrophy of the liver	1, 3, 6, 7, 9, 10	6
Decubitus ulcers of the buttocks or legs	1, 5, 6, 8	4
Lobular pneumonia	1, 2, 3, 4, 7, 9, 11, 13	8
Degeneration of the testicular tubules	2, 5	2
Tubular degeneration of the kidneys	7, 10	2
Pellagrous lesion of the skin	13	1
Ankylostomiasis	8, 11	2
Secondary anemia	5, 9	2
Perihepatitis	11	1
Periportal cirrhosis of the liver	13	1
Scar of the spleen	3, 5	2
Scar of the kidney	6	1
Adenoma of the thyroid	3, 8	2
Infarct of the hypophysis	2	1
Accessory spleen	3	1
Siderosis of the spleen	11, 13	2
Thickening of the mitral valve	12	1
Ulcer of the esophagus and rectum	6	1
Meckel's diverticulum	7	1
Healed periappendicitis	9	1
Kala azar	6	1

The pathologic changes in the nervous system in these cases were as characteristic and uniform in their nature as in their distribution. Primary irritation of the Betz cells and degeneration of the peripheral

nerves, dorsal spinal ganglia, posterior nerve roots and posterior columns were observed almost constantly.

	Case No.	No. of Cases
Nerve cells		
Primary irritation		
Betz cells	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13	12
Nuclei of cranial nerves	1, 2, 3, 4, 5, 8, 11, 13	8
Anterior horn	1, 2, 3, 5, 7, 8, 10, 11, 13	9
Lateral horn	2, 4, 9, 13	4
Diffuse chromatolysis	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13	12
Fatty degeneration	13	1
Shrinkage	1, 2, 3, 4, 5, 6, 7, 10, 12, 13	10
Ischemia	1, 2, 4, 6, 7, 8, 10, 11, 12, 13	10
Severe disintegration	2, 4, 5, 10, 12, 13	6
Nerve fibers		
Central		
Posterior columns	1, 2, 3, 4, 5, 6, 7, 8, 9,* 10,* 13	11
Spinocerebellar tracts	13 *	1
Pyramidal tracts (spinal portion)	13 *	1
Marginal	6,* 7,* 9,* 10,* 13 *	5
Peripheral		
Nerve roots		
Spinal		
Posterior	1 to 13	13
Anterior	1, 2, 3, 4, 6, 7, 10 *	7
Cranial †	1	1
Nerve trunks ‡	1, 5, 6, 7, 8, 9, 10, 13	8
Dorsal spinal ganglia §	6, 7, 9, 10, 13	5

* Marchi stage of degeneration.

† Examination made in only 2 cases (1 and 13).

‡ Examination in only 8 cases (1, 5, 6, 7, 8, 9, 10 and 13).

§ Examined in only 5 cases (6, 7, 9, 10 and 13).

In Nissl picture progressive types of glia cell formation were noted in the posterior columns in 5 cases (3, 4, 5, 6 and 13). The glia was unaffected elsewhere.

Pathologic changes in the vascular system and meninges were distributed as follows:

	Case No.	No. of Cases
Premature arteriosclerosis	9, 10, 13	3
Meningeal hyperplasia	3, 13	2
Meningeal infiltration	4, 6, 10, 12, 13	5
Congestion of blood vessels	3, 4, 5, 9, 10, 11, 12	7
Fresh pial hemorrhage	8, 9	2
Diapedesis in the gray substance	11, 13	2
Anemia	2, 4, 5	3
Perivascular accumulation of pigments	3, 4, 5, 6, 10, 11, 12, 13	8

Certain gradations were noted in the intensity and age of the lesions of the nerve fibers. In 10 of the 11 cases in which degeneration of the fasciculus gracilis was apparent (cases 1, 2, 3, 4, 5, 6, 7, 9, 10 and 13) additional involvement of the fasciculus cuneatus was present. The extent of damage to the latter was much less than to the former. The involvement of the posterior columns was chronic and moderately severe in case 3, subacute and very pronounced in cases 5, 6 and 7, subacute and moderately severe in cases 1 and 2, subacute and less severe in cases 4, 8 and 13 and acute and moderately severe in cases 9 and 10. Except in cases 5 and 8, it was more pronounced in the upper than in the lower segments of the spinal cord. The lesion of the posterior nerve roots was chronic and pronounced in cases 2, 3, 5 and 13, subacute and moderately severe in cases 1, 6 and 7, subacute and less severe in cases 4, 9 and 10 and subacute and very mild in cases 11 and 12. It was more pronounced in the cauda than at the upper levels. The lesion of the anterior nerve roots was much milder than that of the corresponding posterior roots. The changes in the peripheral nerve trunks were more chronic and extensive than those of the posterior nerve roots in the same case, and they appeared to be relatively more pronounced in the lower than in the upper extremities.

COMMENT

In order to establish a proper neuropathologic diagnosis in these cases, I shall consider the specificity and the pathogenesis of the nerve lesions, as well as the etiologic role played by the intestinal disturbance, the tuberculosis and the poor nutritional state.

Pathologic Features.—Primary irritation of the large motor nerve cells has been described in association with various conditions: after separation or injury of the axons (Nissl, Cajal, von Monakow, Spatz and Kohnstein,[9] van Gehuchten[10] and others); senile melancholia (Meyer[11]); dementia of circulatory origin (Cotton and Hammond[12]); syphilitic endarteritis (Nissl, Alzheimer, Jakob[9] and others); spastic

9. Nissl, Cajal, von Monakow, Spatz, Kohnstein, Alzheimer, Jakob and others, cited by Winkelman, N. W.: Beiträge zur Neurohistopathologie der Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

10. van Gehuchten: Pathologische Anatomie der Nervenzellen, in Flatau, E.; Jacobson, L., and Minor, L.: Handbuch der pathologischen Anatomie des Nervensystems, Berlin, S. Karger, 1904.

11. Meyer, A.: Demonstration of Various Types of Changes in the Giant Cells of the Paracentral Lobule, Am. J. Insanity **54**:221, 1897; On Parenchymatous Systemic Degenerations Mainly in the Central Nervous System, Brain **24**:47, 1901.

12. Cotton, H. A., and Hammond, F. S.: Cardiogenetic Psychosis: Report of Case with Autopsy, Am. J. Insanity **67**:467, 1911.

pseudosclerosis (Creutzfeldt [13] and Jakob [14]); dementia paralytica, dementia praecox and Korsakoff's psychosis (Spielmeyer [15]); Landry's paralysis (Jakob [9]); delirium of typhoid (Alzheimer [9]); epidemic cerebrospinal meningitis (Barker [16]); Lissauer's dementia paralytica (Merritt and Springlova [17]); Pick's disease (Williams [18]); acrodynia (Orton and Bender [19] and Patterson and Greenfield [20]); pernicious anemia (Orton and Bender [19]); psychosis following lightning stroke and edema of the brain (Spielmeyer's collection), and beriberi (Peckelharing and Winkler,[21] Wright,[22] Rodenwaldt,[23] Dürck,[24] Kürstermann,[25] Cannon,[26] Eddy and Dalldorf [27] and Weiss and Wilkins [28]). It has been far more constantly observed in cases of pellagra (Babes and

13. Creutzfeldt, H. G.: Ueber eine eigenartige herdförmige Erkrankung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:1, 1920.

14. Jakob, A.: Ueber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde (spastische Pseudosklerose-Encephalomyelopathie mit disseminierten Degenerationsherden), Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:147, 1921.

15. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

16. Barker, L. F.: On Certain Changes in the Cells of the Ventral Horns and of the Nucleus Dorsalis (Clarkii) in Epidemic Cerebrospinal Meningitis, Brit. M. J. **2**:1839, 1897.

17. Merritt, H. H., and Springlova, M.: Lissauer's Dementia Paralytica: A Clinical and Pathological Study, Arch. Neurol. & Psychiat. **27**:987 (May) 1932.

18. Williams, H. W.: The Peculiar Cells of Pick's Disease: Their Pathogenesis and Distribution in Disease, Arch. Neurol. & Psychiat. **34**:508 (Sept.) 1935.

19. Orton, S. T., and Bender, L.: Lesions in the Lateral Horns of the Spinal Cord in Acrodynia, Pellagra and Pernicious Anemia, Bull. Neurol. Inst. New York **1**:506, 1931.

20. Patterson, D., and Greenfield, J. G.: Erythroedema Polyneuritis, Quart. J. Med. **17**:6, 1923.

21. Peckelharing, C. A., and Winkler, C.: Mitteilung über die Beriberi, Deutsche med. Wchnschr. **13**:845, 1887.

22. Wright, H.: Beiträge zur Kenntnis der Beriberi, Arch. f. Schiffs- u. Tropenhyg. **9**:518, 1905.

23. Rodenwaldt: Pathologische Anatomie des Nervensystems bei Beriberi, Arch. f. Schiffs- u. Tropenhyg. (supp. 5) **12**:31, 1908.

24. Dürck, H.: Untersuchungen über die pathologische Anatomie der Beriberi, Beitr. z. path. Anat. u. z. allg. Path., 1908, supp. 8, p. 1.

25. Kürstermann: Zur Pathologie der Beriberi, München. med. Wchnschr. **43**: 436, 1896.

26. Cannon, A.: The Pathology of Beriberi, Tr. Roy. Soc. Trop. Med. & Hyg. **23**:263, 1929.

27. Eddy, W. H., and Dalldorf, G.: The Avitaminoses, Baltimore, Williams & Wilkins Company, 1937.

28. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937.

Sion,[29] Parhon and Papinian,[30] Gregor,[31] Lukács and Fabinyi,[32] Report of Pellagra Commission of the State of Illinois,[33] Anderson and Spiller,[34] Kozowsky,[35] Rezza,[36] Mott,[37] Singer and Pollock,[38] Vedder,[39] Pierce,[40] Denton,[41] Ostertag,[42] Winkelman,[43] Pentschew,[44] Klauder and Winkelman,[45] Szarvas, Stief and Dancz, [46] Langworthy,[47] Beyer,[48] Orton and Bender,[19] Marinescu,[49] Bumke and Kraft,[50] Eddy and Dalldorf,[27]

29. Babes, V., and Sion, V.: Die Pellagra, in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1901, vol. 24, pt. 2, sect. 3.

30. Parhon, R., and Papinian, J.: Note sur les altérations des neurofibrilles dans la pellagra, Compt. rend. Soc. de biol. **58**:360, 1905.

31. Gregor, A.: Beiträge zur Kenntnis der pellagrösen Geistesstörungen, Jahrb. f. Psychiat. u. Neurol. **28**:215, 1907.

32. Lukács, H., and Fabinyi, R.: Zur pathologischen Anatomie der Pellagra, Allg. Ztschr. f. Psychiat. **65**:657, 1908.

33. Clinical and Pathological Studies, in Report of the Pellagra Commission of the State of Illinois, 1911, p. 16.

34. Anderson, P. V., and Spiller, W. G.: Pellagra with a Report of Two Cases with Autopsy, Am. J. M. Sc. **141**:94, 1911.

35. Kozowsky, A. D.: Die Pellagra. Pathologisch-anatomische Untersuchung, Arch. f. Psychiat. **49**:204, 556 and 873, 1912.

36. Rezza, A.: Beitrag zur pathologischen Anatomie der Pellagra-Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:1, 1912.

37. Mott, F. W.: The Histological Changes in the Nervous System of Dr. Box's Case of Pellagra, Brit. M. J. **2**:4, 1913.

38. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. **11**:565 (June) 1913.

39. Vedder, E. B.: Dietary Deficiency as the Etiological Factor in Pellagra, Arch. Int. Med. **18**:137 (Aug.) 1916.

40. Pierce, L. B.: Pellagra: Report of a Case, Am. J. Psychiat. **4**:237, 1924.

41. Denton, J.: The Pathology of Pellagra, Am. J. Trop. Med. **5**:173, 1925.

42. Ostertag, B.: Zur Pathologie der akuten Pellagra-Psychosen, Centralbl. f. d. ges. Neurol. u. Psychiat. **40**:127, 1925.

43. Winkelman, N. W.: Beiträge zur Neurohistopathologie der Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

44. Pentschew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:17, 1928.

45. Klauder, J. V., and Winkelman, N. W.: Pellagra Among Chronic Alcoholic Addicts: A Clinical and Laboratory Study, J. A. M. A. **90**:364 (Feb. 4) 1928.

46. Szarvas, A.; Stief, A., and Dancz, M.: Contribution au tableau clinique de la pellagre et à son histopathologie, avec considération particulière du système extrapyramidal, Schweiz. Arch. f. Neurol. u. Psychiat. **28**:139, 1931.

47. Langworthy, O. R.: Lesions of the Central Nervous System Characteristic of Pellagra, Brain **54**:291, 1931.

48. Beyer, A.: Histopathologie der Pellagra, Arch. f. Psychiat. **98**:294, 1932.

49. Marinescu, S. D.: Pellagra-Studien in Rumänien, Zentralbl. f. d. ges. Neurol. u. Psychiat. **73**:246, 1934.

50. Bumke, O., and Kraft, E.: Pellagra, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 795.

Stepp,[51] Greenfield and Holmes,[52] Sundwall,[53] Crane-Lillie and Rhoads,[54] Zimmerman and Burack [55] and others).

Although the terms primary irritation, axonal reaction and retrograde degeneration were designed originally for a peculiar type of degeneration of the ganglion cells produced by damage of the axis-cylinders, there were many instances in which no morphologic alteration of the latter could be demonstrated. One may doubt the existence of any unity of genesis, although the degeneration might possibly be a physiologic axonal reaction. Since it occurs in so wide a variety of diseases, it seems hardly to be pathognomonic, especially in view of the limited forms of response which the nerve tissue shows to different types of noxious agents. However, one may suspect a common underlying factor in the occurrence of this kind of cellular change in various conditions, for instance, an intracellular metabolic disturbance. Unfortunately, these questions cannot be answered with satisfaction merely by morphologic studies. In my series there were instances (1, 2 and 10) to support the original conception of primary irritation. However, in 3 cases (3, 4 and 7) the axons but not their mother cells were damaged, whereas in 5 other cases (5, 7, 8, 11 and 13) this type of cell change occurred without demonstrable alteration of the axons. Whatever the genesis may be, the constant manifestation of this phenomenon in a group of cases like the present series is certainly characteristic of pellagra.

Posterior sclerosis without concomitant involvement of the lateral tracts is characteristic of tabes dorsalis but can occur, though less often, as mentioned by Tuczek,[56] in pernicious anemia, diabetes mellitus, alcoholism, arsenic poisoning, leprosy, ergotism and dementia paralytica. It has been described also in cases of human beriberi (Peckelharing and Winkler,[21] Mendès,[57] Wright,[22] Rodenwaldt,[23] Dürck [24] and Schüff-

51. Stepp, W.: Ernährungslehre, Grundlagen und Anwendung, Berlin, Julius Springer, 1939.

52. Greenfield, J. G., and Holmes, J. M.: A Case of Pellagra: Pathological Changes in Spinal Cord, Brit. M. J. **1**:815, 1939.

53. Sundwall, J.: Tissue Alteration in Malnutrition and Pellagra, Hygienic Laboratory Bulletin 106, United States Treasury Department, Public Health Service, 1917, p. 5.

54. Crane-Lillie, M., and Rhoads, C. P.: Pathology of the Central Nervous System in Canine Black Tongue, Arch. Path. **18**:459 (Oct.) 1934.

55. Zimmerman, H. M., and Burack, E.: Lesions of the Nervous System Resulting from Deficiency of the Vitamin B Complex, Arch. Path. **13**:207 (Feb.) 1932.

56. Tuczek, F.: Ueber die nervösen Störungen bei der Pellagra, Deutsche med. Wchnschr. **14**:222, 1888; Klinische und anatomische Studien über die Pellagra, Berlin, Gustav Fischer, 1893.

57. Mendès, P., cited by Dürck.[24]

ner [58]), experimental vitamin B_1 deficiency (Lukács and Fabinyi [32] and Zimmerman and Burack [55]), experimental vitamin A deficiency (Zimmerman [59] and Mellanby [60]), pellagra (Tuczek,[56] Sandwith,[61] Babes and Sion,[29] Winkelman [43] and Tucker [62]), pellagra secondary to carcinoma of the stomach (O'Leary [63] and Eusterman and O'Leary [64]), and experimental vitamin B_2 deficiency (Zimmerman and Burack,[65] Zimmerman, Cowgill, Bunnell and Daun,[66] Zimmerman, Cowgill and Fox [67] and Gildea, Castle, Gildea and Cobb [68]). Posterolateral sclerosis is of course characteristic of pernicious anemia but is observed not infrequently in cases of pellagra (Verga,[69] Bouchard,[70] Bouchard,[71] Tonnini,[72] Neus-

58. Schüffner, W.: Mangel an den Vitaminen des B-Komplexes, in Stepp,[51] p. 372.

59. Zimmerman, H. M.: Lesions of the Nervous System in Vitamin Deficiency: Rats on a Diet Low in Vitamin A, J. Exper. Med. **57**:215, 1933.

60. Mellanby, E.: The Experimental Production and Prevention of Degeneration in the Spinal Cord, Brain **54**:247, 1931; Lesions of the Central and Peripheral Nervous Systems Produced in Young Rabbits by Vitamin A Deficiency and a High Cereal Intake, ibid. **58**:141, 1935.

61. Sandwith, F. M.: Three Fatal Cases of Pellagra with Examination of the Spinal Cords, J. Path. & Bact. **7**:460, 1901.

62. Tucker, B. R.: The Neuropathology of Pellagra in Its Relation to the Cutaneous and Other Manifestations, South. M. J. **28**:603, 1935.

63. O'Leary, P. A.: Secondary Types of Pellagra, M. Clin. North America **10**:647, 1926.

64. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract, Arch. Int. Med. **47**:633 (April) 1931.

65. Zimmerman, H. M., and Burack, E.: Studies on the Nervous System in Deficiency Diseases: II. Lesions Produced in the Dog by Diets Lacking the Water-Soluble, Heat-Stable, Vitamin B_2 (G), J. Exper. Med. **59**:21, 1934.

66. Zimmerman, H. M.; Cowgill, G. R.; Bunnell, W. W., and Daun, M.: Studies on the Nervous System in Deficiency Diseases: Experimental Blacktongue, Am. J. Physiol. **109**:440, 1934.

67. Zimmerman, H. M.; Cowgill, R. G., and Fox, J. C., Jr.: Neurologic Manifestations in Vitamin G (B_2) Deficiency: An Experimental Study in Dogs, Arch. Neurol. & Psychiat. **37**:286 (Feb.) 1937.

68. Gildea, M. C. L.; Castle, W. B.; Gildea, E. F., and Cobb, S.: Neuropathology of Experimental Vitamin Deficiency: A Report of Four Series of Dogs Maintained on Diets Deficient in the B Vitamins, Am. J. Path. **11**:669, 1935.

69. Verga: Richerche necroscopiche sulla pellagre, Gaz. med. ital. Lomb. **1**: 203, 1862.

70. Bouchard, C.: Recherches nouvelles sur la pellagre. Anatomie pathologique, Paris, F. Savy, 1862, p. 145.

71. Bouchard, C.: Etude d'anatomie pathologique sur un cas de pellagre, Compt. rend. Soc. de biol. **1**:51, 1864.

72. Tonnini, S.: I disturbi spinali nei pazzi pellagrosi, anatomia pathologica, Riv. sper. di freniat. **9**:208, 1883; **10**:63, 1884.

ser,[73] Marchi,[74] Belmondo,[75] Lombroso,[76] Tuczek,[56] Gaucher and Sergent,[77] Sereni,[78] Gregor,[31] Kozowsky,[35] Pentschew,[44] Szarvas, Stief and Dancz,[46] Marinescu,[49] Guillain, Bertrand, Mollaret and Lereboullet,[79] Bumke and Kraft,[50] Eddy and Dalldorf,[27] Stepp [51] and Greenfield and Holmes [52]), experimental B_2 deficiency (Gildea, Wattwinkel and Castle,[80] Crane-Lillie and Rhoads [54] and Zimmerman and Burack [65]), lathyrism (Le Roy de Méricourt [81]), sprue (Reed and Ash [82]), experimental vitamin E deficiency (Einarson and Ringsted [83]), diabetes mellitus (Meyer [84]) and poisoning with aluminum (Döllken [85]) and with mercury (Tirelli [86]). In spite of a great variety of conditions in which the posterior sclerosis with or without involvement of the lateral tracts may take place, the causative factors are probably fewer, and the disturbances may owe their origin to a vitamin deficiency as a common underlying or contributory cause.

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73. Neusser, E.: Untersuchungen über die Pellagra, Wien. med. Wchnschr. **37**:132, 1887; Vortrag über die Pellagra in Osterreich und Rumänien, Anz. d. k. k. Gesellsch. d. Aerzte in Wien, 1887, p. 19.

74. Marchi, V.: Richerche anatomo-pathologiche e bacteriologiche sul tifo pellagroso, Riv. sper. di freniat. **14**:341, 1888.

75. Belmondo, E.: Le alterazione anatomiche del midollo spinale nella pellagra, Riforma med. **5**:1532, 1889; abstracted, Centralbl. f. allg. Path. u. path Anat. **1**:300, 1890.

76. Lombroso, C.: Die Lehre von der Pellagra, Berlin, 1898, p. 132.

77. Gaucher, and Sergent, E.: Note sur les lésions histologiques viscérales de la pellagre, Bull. Soc. méd. d. hôp. de Paris **12**:552, 1895.

78. Sereni, S.: Alterazioni istologiche del midollo spinale causate da veleni maidici, Riv. sper. di freniat. **33**:190, 1907.

79. Guillain, G.; Bertrand, I.; Mollaret, P., and Lereboullet, J.: Etude anatomique d'un cas français de pellagre avec paraplégie, Bull. Soc. méd. d. hôp. de Paris **50**:650, 1934.

80. Gildea, E. F.; Wattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

81. Le Roy de Méricourt, A., cited by Dürck.[24]

82. Reed, A. C., and Ash, J. E.: Atypical Sprue, Arch. Int. Med. **40**:787 (Dec.) 1927.

83. Einarson, L., and Ringsted, A.: Effect of Chronic Vitamin E Deficiency on the Nervous System and Skeletal Musculature in Adult Rat, London, Oxford University Press, 1938.

84. Meyer, A.: Zur Frage der diabetischen Nephrose und Polyneuritis, Ztschr. f. klin. Med. **122**:688, 1932.

85. Döllken: Ueber die Wirkung des Aluminiums mit besonderer Berücksichtigung der durch das Aluminium verursachten Läsionen im Central Nervensystem, Arch. f. exper. Path. u. Pharmakol. **40**:98, 1898.

86. Tirelli, V.: Sur l'anatomie pathologique des éléments nerveux dans l'empoisonnement aigu par le sublimé, Arch. ital. de biol. **26**:230, 1896.

There has been little dispute about the primary nature of the lateral sclerosis. As to its histopathogenesis, there has been just as much evidence to suggest a primary as a secondary phenomenon (Peckelharing and Winkler,[21] Marchi,[74] Belmondo,[75] Tuczek,[56] Mendès,[57] Lombroso,[76] Sandwith,[61] Babes and Sion,[20] Gregor,[31] Rodenwaldt,[23] Lukács and Fabinyi,[32] Dürck,[24] Roberts,[87] Kozowsky,[35] Mott,[37] Winkelman,[43] Langworthy,[47] Zimmerman and Burack,[65] Zimmerman,[59] Marinescu,[49] Crane-Lillie and Rhoads,[54] Zimmerman, Cowgill, Bunnell and Daun,[66] Zimmerman, Cowgill and Fox,[67] Eddy and Dalldorf,[27] Greenfield and Holmes[52] and others). Since the lesion of the posterior columns in the present cases had not yet reached the terminal stage, the question of primary or secondary degeneration cannot be answered by the type of gliosis, whether anisomorphic or isomorphic. Nevertheless, the fact that there was no single case of posterior sclerosis in which the posterior nerve roots were not involved and that the posterior columns remained unaltered in cases 11 and 12, in which the posterior nerve roots were only slightly damaged, indicates beyond a doubt a secondary process in the sense of a wallerian degeneration. On the other hand, the extensiveness and completeness of the lesion of the posterior columns, as shown in case 3, imply that the nerve fibers affected were those not merely of the extrinsic but of the intrinsic group as well. The apparent accentuation of the process at an upper level of the spinal cord (cases 1, 2, 3, 4, 6, 7, 9, 10 and 13) does not necessarily indicate a regional predilection but rather is in accord with the theory of wallerian degeneration. Apparently, this accentuation at higher levels may be attributed to the normal variation in the density of the nerve fibers in the posterior columns, which become more compact at the higher levels.

Although in several respects the posterior sclerosis in the present cases resembled that of tabes dorsalis and pernicious anemia, there were more features to speak against such a diagnosis. As in tabes dorsalis, the posterior nerve roots, Lissauer's zone and the cornu radicularis were involved in the cases reported here. But in contrast to what is seen in tabes, in these cases alteration of the cornu-commissure zone and the posterior internal zone, degeneration of the gray substance, damage to the anterior nerve roots and the whole primary sensory neuron and apparent local prominence of the process at a higher level of the spinal cord (Marie[88]) were observed. Furthermore, there was

87. Roberts, S. R.: Pellagra, St. Louis, C. V. Mosby Company, 1912; cited by Vedder.[39]

88. Marie, M.: De l'origine exogène ou endogène des lésions du cordon postérieur etudiées comparativement dans le tabès et dans la pellagre, Semaine méd. **14**:17, 1894.

no significant change in the meninges, no serologic reaction for syphilis and no syphilitic lesions elsewhere in the body. As in pernicious anemia, I observed in these cases early involvement of the central region of the posterior columns and apparent accentuation of the process at the higher segments of the spinal cord. But the degeneration of the nerve cells in the anterior and lateral horns, the constant involvement of the sensory nerve roots and the peripheral nerves, the absence of a lacunar appearance of the posterior columns, the absence of conspicuous megaloblasts in the bone marrow and of iron-containing pigments in the various organs and the apparent normal mucosa of the stomach spoke strongly against the diagnosis of pernicious anemia. Furthermore, pernicious anemia is a rare disease in China. Sprue also can be excluded. For obvious reasons, it is scarcely necessary to mention in the differential diagnosis in the present cases such possibilities as carcinoma of the gastrointestinal tract, gastroenterostomy, gastrectomy, alcoholism, diabetes mellitus, metallic poisoning, leprosy, lathyrism, ergotism and dementia paralytica. Considering the changes in the cord and the characteristic degeneration of the ganglion cells, I am of the opinion that the condition in my cases probably is one of avitaminosis, for instance beriberi or pellagra, rather than any other disease.

Clinically Cobb and Coggeshall [89] pointed out that the principal causes of polyneuritis are virus, bacteriotoxic and chemical agents and deficiencies or metabolic disturbances. Under the category of conditions caused by or contributing to a state of deficiency, they included pellagra, beriberi, pernicious anemia, sprue, chronic colitis, chronic bacillary dysentery, tuberculosis with cachexia, cancer with cachexia, diabetes mellitus, senility with cachexia, pregnancy, pernicious vomiting, hunger edema, myxedema and hematoporphyrinuria. Obviously, the polyneuritis in my cases should belong to certain classes in this group. Morphologically the changes of the peripheral nerves were notably uniform, so much so that it was hardly possible to ascertain the cause from a study of the lesions alone. Nevertheless, a general clue may be obtained if the distribution of the process and the type of the tissue affected are considered. The selective nature of certain forms of neuritis can be illustrated by the predominant involvement of the cranial nerves in diphtheria, of the radial nerves in lead poisoning, of the visceral and vasomotor nerves and of the nerves in the lower extremities in beriberi, of the sensory fibers in avitaminosis, diabetes mellitus and arsenic poisoning and of the motor fibers in poisoning with lead, mercury and bismuth. In our cases the damage of the sensory component of the peripheral nerves was far more pronounced than that of the motor, and

89. Cobb, S., and Coggeshall, N. C.: Neuritis, J. A. M. A. **103**:1608 (Nov 24) 1934.

it was more intensive in the lower extremities than in the upper, being least striking in the cranial nerves. Therefore, from the pathologic point of view, the neuritic process in my cases is, indeed, suggestive of a deficiency.

Although my associates and I did not study the sympathetic nerve chains and the visceral and vasomotor nerves, the characteristic change in the ganglion cells in the lateral horns, the brain stem and the subthalamicum was indicative of a disturbance of the autonomic nervous system. Degeneration of the autonomic nervous system has been described in cases of beriberi by Kürstermann, [25] Ellis,[90] Wright,[22] Rodenwaldt,[23] Miura,[91] Findlay,[92] McCarrison,[93] Cannon,[26] Weiss and Wilkins,[28] Eddy and Dalldorf [27] and others; in cases of pellagra by Bassi,[94] Marchi,[74] Lombroso,[76] Singer and Pollock,[38] Brugia,[95] Ostertag,[42] Orton and Bender,[19] Tucker [62] and others; and in cases of pernicious anemia by Orton and Bender.[19] It was taken as a sign to support the hypothesis that pellagra is a virus disease (Orton and Bender [19] and Tucker [62]) and to account for the cutaneous changes in pellagra (Dejerine [96] and Rosentoul [97]) and the lesions of the cardiac and digestive systems in beriberi and pellagra. The nonspecific colitis in cases 3 and 13 might be correlated with the involvement of the autonomic nervous system, but the lesion of the intestine in the other cases was of specific origin and there was no ulcer of the stomach or dilatation of the heart. The cutaneous change in case 13 might be suspected to be trophic, but there was complete absence of an inflammatory process characteristic of a virus disease.

In view of the fact that many factors may operate in the production of a diffuse change in the ganglion cells in the form of chromatolysis, shrinkage, ischemia and severe disintegration, one can hardly ever make use of these changes to diagnose a disease. Of course, they have been

90. Ellis, W. G.: A Contribution to the Pathology of Beriberi, Lancet **2**:985, 1898.

91. Miura, K.: Beriberi oder Kakke, Ergebn. d. inn. Med. u. Kinderh. **4**:280, 1909.

92. Findlay, G. M.: An Experimental Study of Avian Beriberi, J. Path. & Bact. **24**:175, 1921.

93. McCarrison, R.: Studies in Deficiency Diseases, London, Oxford University Press, 1921.

94. Bassi, G., cited by Sundwall.[53]

95 Brugia: Die Veränderungen des Gangliensystems des Sympathicus bei der Pellagra-Geistesstörung, Centralbl. f. allg. Path. u. path. Anat. **14**:692, 1903.

96. Dejerine, J.: Sur les altérations des nerfs cutanés dans la pellagre, Compt. rend. Acad. d. sc. **93**:91, 1881.

97. Rosentoul, M. A.: Changes in Skin Nerves at Pellagra, Acta dermat.-venereol. **15**:495, 1934.

frequently observed in cases of beriberi and pellagra. I am, however, of the opinion that in the present cases they probably indicated a combined effect of deficiency, inanition, hydration and agonal circulatory disturbance.

As observed in my cases, the fresh hemorrhages of the meninges and the nerve parenchyma have been recorded in cases of human beriberi by Dürck [24] and Weiss and Wilkins [28]; in cases of experimental B_1 deficiency by Hofmeister,[98] Pappenheimer and Goettsch,[99] Prickett,[100] Alexander, Pijoan, Myerson and Keane [101] and Alexander,[102] and in cases of pellagra by Tonnini,[72] Neusser,[73] Gregor [31] and Bassi.[94] They may represent also an agonal phenomenon; nevertheless, the possibility of a deficiency in the antiangiodegenerative factor of vitamin B_1 and in vitamin C should not by any means be overlooked.

The so-called premature arteriosclerosis shows essentially the same morphologic appearance as the senile type. The former differs from the latter only in the age at which it is observed. Whatever the etiologic factors may be, toxic or metabolic, it represents a slowly developing regressive process. Yamagiwa [103] observed this kind of change in cases of beriberi and interpreted it as primary damage. He expressed the opinion that the neurodegeneration is secondary. Bouchard,[70] Paussie,[104] Belmondo,[75] Tuczek,[56] Sergent,[105] Zartarian,[106] Brugia,[95] Anderson and Spiller,[34] Kozowsky,[35] Bassi,[94] Pierce,[40] Denton,[41] Winkelman,[43] Pentschew,[44] Harris,[107] Szarvas, Stief and Dancz,[46] Beyer,[48] de Morsier and Starobinski,[108] Marinescu,[49] Guillain, Bertrand, Mollaret and Lereboullet,[79] Bumke and Kraft [50] and Stepp [51] observed it in cases of pellagra and concluded it was either an independent or a fundamental

98. Hofmeister, F.: Studien über qualitative Unterernährung, Biochem. Ztschr. **128**:540, 1922.

99. Pappenheimer, A. M., and Goettsch, M.: A Cerebellar Disorder in Chicks, Apparently of Nutritional Origin, J. Exper. Med. **53**:11, 1931.

100. Prickett, C. O.: The Effect of a Deficiency of Vitamin B_1 upon the Central and Peripheral Nervous Systems of the Rat, Am. J. Physiol. **107**:471, 1934.

101. Alexander, L.; Pijoan, M.; Myerson, A., and Keane, H. M.: Beriberi and Scurvy: An Experimental Study, Tr. Am. Neurol. A. **64**:135, 1938.

102. Alexander, L.: Wernicke's Disease, Am. J. Path. **16**:61, 1940.

103. Yamagiwa, K.: Beiträge zur Kenntnis der Kakke (Beriberi), Virchows Arch. f. path. Anat. **156**:451, 1899.

104. Paussie, cited by Kozowsky.[35]

105. Sergent, E.: L'atrophie des viscéres et l'hypoplasie artérielle dans la pellagre, Presse méd. **9**:1, 1901.

106. Zartarian, D., cited by Kozowsky.[35]

107. Harris, cited by Pentschew.[44]

108. de Morsier, G., and Starobinski, A.: Un cas de pellagre nerveuse à Génève. Considérations sur la pellagre sporadique, Rev. méd. de la Suisse Rom. **51**:763, 1931; abstracted, Centralbl. f. d. ges. Neurol. u. Psychiat. **63**:835, 1932.

pathologic process. In my cases it seemed to exist as a concomitant change rather than to play a determinant role in the causation of the nerve lesions.

Slight lymphocytic infiltration and hyperplasia of the meninges have been not infrequently noted in association with beriberi and pellagra, but appeared to be noncharacteristic and should not be overstressed in the histopathogenetic interpretation (Paussie,[104] Verga,[69] Tonnini,[72] de Hieronimis,[109] Tuczek,[56] Belmondo,[75] Pierce,[40] Lombroso,[76] Brugia,[95] Hirsch,[110] Szarvas, Stief and Dancz,[46] Nauck,[111] Bumke and Kraft [50] and Eddy and Dalldorf [27]).

Mild accumulation of the lipoid pigments in the perivascular spaces is likewise too often observed to signify anything other than a process of wear and tear in the nervous system.

In brief, the nerve lesions in this series of cases were essentially degenerative and involved diffusely both the sensorimotor and the autonomic nervous system. There was a triad of characteristic pathologic features, namely, damage of the peripheral nerve trunks and the nerve roots, degeneration of the spinal funiculi, especially the posterior columns, and primary irritation of the large motor nerve cells and the vegetative nuclei. On the one hand, some of these changes exhibited a cause and effect relation. The primary irritation of the anterior horn cells, and perhaps also of the lateral horn cells, and the degeneration of the ascending fibers of the spinal cord evidently followed the damage of the nerve roots and the peripheral nerve trunks. Judging from the distribution and the variation in the intensity of the peripheral lesions, I agree with Zimmerman [112] that the primary damage acted chiefly on the sensory neurons, especially on their distal portions in the lower extremities. On the other hand, there were features indicative of a primary or independent process. The primary irritation of the Betz cells, and perhaps also of the vegetative nuclei in the brain stem, and the involvement of the lateral tracts and the endogenous fibers of the posterior columns could not be accounted for on a secondary basis. Therefore, in my cases there were both primary and secondary degenerations, which in one sense were systematic and in another represented an ascending phenomenon. As previously mentioned, each of the pathologic features may make its appearance alone in many conditions,

109. de Hieronimis, cited by Kozowsky.[35]

110. Hirsch, cited by Sundwall.[53]

111. Nauck, E. G.: Beitrag zur Pathologie und Epidemiologie der Pellagra, Centralbl. f. d. ges. Neurol. u. Psychiat. **68**:668, 1933.

112. Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiencies, Yale J. Biol. & Med. **12**:23, 1939.

but when they are considered together, one suspects beriberi and pellagra as the most probable diagnoses.

Comparison with some of the neuropathologic reports on human and experimental beriberi and pellagra tends to establish the correctness of my diagnosis.

Human Beriberi.—Baelz [113] and Scheube [114] called the neuritic process endemic multiple neuritis, and they also observed atrophy of the anterior horn cells. Peckelharing and Winkler [21] described degeneration of the peripheral nerves, including those of the skin and muscles, total demyelination of the posterior lumbar and sacral nerve roots, bilateral ascending degeneration in the spinal cord, primary irritation of the anterior horn cells and obliteration of the central canal. Miura [115] noted vacuolation of the anterior horn cells but no change in the peripheral nerves and the fiber tracts. Kürstermann [25] recorded degeneration of the peripheral nerves and muscles, increase of neurilemma nuclei in the intervertebral ganglia and vacuolation of the anterior horn cells. Ellis [90] demonstrated changes in the peripheral nerves of the paralytic type and changes in the sympathetic and parasympathetic nerves of the moist type. Yamagiwa [103] stressed the occurrence of thickening of the blood vessels in the peripheral nerves as a fundamental process in the degeneration of the nerve fibers. Rumpf and Luce [116] described chronic lipomatous interstitial neuritis, fresh degeneration of the posterior nerve roots and the white substance throughout the spinal cord and atrophy of the anterior horn cells. Wright [22] found in cases of acute involvement neuritis of the terminal portions of the sensorimotor and autonomic neurons, with axonal reaction of their parent cells, and in cases of chronic disturbance degeneration of the fasciculus gracilis in the lumbar and sacral segments. Ballet [117] noted atrophy of the anterior horn cells. Mendès [57] described neuritis of the peripheral nerves and the anterior and posterior nerve roots, atrophy of the nerve cells of the spinal cord and degeneration of the fasciculus gracilis. Dürck [24] noted in cases of chronic damage the existence of degeneration of the posterior nerve roots and sclerosis of the posterior columns and the spino-

113. Baelz, E.: Ueber die in Japan vorkommenden Infektions-Krankheiten, Mitth. d. deutsch. Gesellsch. f. Nat.- u. Völkerkunde Ostasiens **3**:295, 1882; Ztschr. f. klin. Med. **4**:616, 1882.

114. Scheube, B.: Klinische Beobachtungen über die Krankheiten Japans, Virchows Arch. f. path. Anat. **99**:522, 1885; Die japanische Kakke (Beriberi), Deutsches Arch. f. klin. Med. **31**:141 and 307, 1882; **32**:83, 1883.

115. Miura, M.: Beiträge zur pathologischen Anatomie der Kakke, Virchows Arch. f. path. Anat. **111**:361, 1888.

116. Rumpf and Luce: Zur Klinik und pathologischen Anatomie der Beriberikrankheit, Deutsche Ztschr. f. Nervenh. **18**:63, 1900.

117. Ballet, cited by Dürck.[24]

cerebellar tracts, in addition to peripheral neuritis, tigrolysis of the anterior horn cells and Clarke's columns and fresh hemorrhages in the gray substance of the spinal cord. Rodenwaldt [28] noted degeneration of the peripheral nerves and the posterior columns and primary irritation of the nerve cells in the anterior horns, the lateral horn and Clarke's columns. Miura [115] mentioned that the special point of attack was in the peripheral nerves and muscles, while the spinal cord, the nerve roots and the sympathetic nervous system might sometimes be affected, but the brain always remained intact. Vedder [118] found in the spinal cord alteration of the nerve cells and scattered foci of degeneration of the white substance. Cannon [26] observed edema of the brain, swelling and vacuolation of the cortical nerve cells, degeneration of the sensorimotor and parasympathetic nerves and primary irritation of the anterior horn cells. Weiss and Wilkins [28] observed primary irritation of the nerve cells in the vagus centers and widespread perivascular hemorrhages in the brain. Eddy and Dalldorf [27] summarized the changes as neuritis of the peripheral nerves, cranial nerves and vagus system, occasional hyperplasia of the meninges, degeneration of the ganglion cells in the pons, medulla and spinal cord and fatty degeneration of occasional fibers in the spinal cord and brain. They commented that the nerves supplying the lower extremities were most commonly affected and the peripheral portions of the nerves were first and most seriously altered. Williams and Spies [119] expressed the opinion that the peripheral neuritis, congestion of the meninges, congestion and softening of the brain and spinal cord and diffuse degeneration of the ganglion cells were the common lesions in the nervous system. Schüffner pointed out that although isolated vacuolation of the anterior horn cells and degeneration of the posterior column were observed, the nutritional damage primarily attacked the nerves and muscles.

Experimental Beriberi.—Eijkman [120] observed in fowls peripheral neuritis and degeneration of the anterior horn cells, with the nerve roots intact. Shiga and Kusama [121] were able to produce polyneuritis in monkeys, Andrews [122] in puppies and Voegtlin and Lake [123] in cats and

118. Vedder, cited by Vedder.[39]

119. Williams, R. R., and Spies, T. D.: Vitamin B_1 (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938.

120. Eijkman, C.: Eine Beriberi-ähnliche Krankheit der Hühner, Virchows Arch. f. path. Anat. **148**:523, 1897.

121. Shiga, K., and Kusama, S.: Ueber die Kakke- (Beriberi) ähnliche Krankheit der Tiere (Studien über das Wesen der Kakke), Arch. f. Schiffs- u. Tropenhyg. (supp. 3) **15**:5, 1911.

122. Andrews, V. L.: Infantile Beriberi, Philippine J. Sc., Sect. B **7**:67, 1912.

123. Voegtlin, C., and Lake, G. C.: Experimental Mammalian Polyneuritis Produced by a Deficient Diet, Am. J. Physiol. **47**:558, 1919.

dogs. Fraser and Stanton [124] noted typical wallerian degeneration of the peripheral nerves in fowls. Rats were resistant to lesions of the peripheral nerves (Schaumann,[125] Hofmeister,[98] Kingery and Kingery,[126] Stern and Findlay,[127] Grinker and Kandel [128] and Prickett [100]). Vedder and Clark [129] and Kimura [130] mentioned that the degeneration of the nerve cells and fibers was widespread and that the latter could affect not only the peripheral nerves and roots but all the tracts of the spinal cord, medulla, pons, midbrain and internal capsule. Findlay [92] demonstrated chromatolysis of the nerve cells, including those of the ganglia in the adrenal glands, degeneration of the peripheral nerves, including the vagus and the nerve plexus of the intestine, and a positive Marchi reaction in the brain and spinal cord. McCarrison [93] demonstrated degeneration of Auerbach's plexus. Hofmeister [98] observed hemorrhages in the cerebrum, brain stem and cerebellum in rats. Ma [131] revealed alteration of the mitochondria of the spinal ganglion cells of fowls. Woolard [132] demonstrated degeneration of the sensorimotor nerve endings in the muscles of rats. Culley [133] expressed the belief that the changes in the peripheral nerves of fowls fed on polished rice were not identical with wallerian degeneration. Tsunoda and Kura [134] noted early lesions in the form of cloudy swelling of the terminations of the sensorimotor nerves.

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124. Fraser, H., and Stanton, A. T.: Collected Papers on Beriberi, in Studies from the Institute for Medical Research, Federated Malay States, London, John Bale Sons & Danielsson, Ltd., 1924, no. 17.

125. Schaumann, H.: Die Ätiologie der Beriberi unter Berücksichtigung des gesamten Phosphorstoffwechsels, Arch. f. Schiffs- u. Tropenhyg. (supp. 8) **14**:11, 1910; Weitere Beiträge zur Ätiologie der Beriberi, ibid. (supp.) **16**:137, 1912.

126. Kingery, H. M., and Kingery, J. R.: A Study of the Nervous Tissues of Albino Rats Fed on a Vitamin-Free Diet, Anat. Rec. **29**:364, 1925.

127. Stern, R. O., and Findlay, G. M.: The Nervous System in Rats Fed on Diets Deficient in Vitamin B_1 and B_2, J. Path. & Bact. **32**:63, 1929.

128. Grinker, R. R., and Kandel, E.: Experimental Vitamin (A, B_1, B_2 and B Complex) Deficiency, Arch. Neurol. & Psychiat. **30**:1287 (Dec.) 1933.

129. Vedder E. B., and Clark, E.: A Study of Polyneuritis Gallinarum: A Fifth Contribution to the Etiology of Beriberi, Philippine J. Sc., Sect. B **7**:423, 1912.

130. Kimura, O.: Ueber die Degenerations—und Regenerations—vorgänge bei der sogenannten "Reisneuritis" der Vögel, Deutsche Ztschr. f. Nervenh. **64**:153, 1919.

131. Ma, W. C.: A Study of the Mitochondrial Elements of the Spinal Ganglion Cells of Beriberi Fowls, Am. J. Anat. **36**:215, 1925.

132. Woolard, H. H.: The Nature of the Structural Changes in Nerve Endings in Starvation and in Beriberi, J. Anat. **61**:283, 1927.

133. Culley, P. G.: Polyneuritis in Fowls: Its Peripheral Nervous Lesions as Compared with Wallerian Degeneration, Quart. J. Exper. Physiol. **17**:65, 1927.

134. Tsunoda, T., and Kura, N.: Experimentelle Studien über die morphologischen Veränderungen der Hautnervenendigungen bei der Vogelberiberi oder Reiskrankheit, Virchows Arch. f. path. Anat. **267**:421, 1928.

Pappenheimer and Goettsch [99] observed in chickens edema, necrosis and hemorrhages in the cerebellum. Zimmerman and Burack observed demyelination of the peripheral nerves and minimal lesions of the same variety in the fasciculus gracilis. Prickett[100] noted hemorrhages in the brain of rats and emphasized that the site of the lesion in the beriberi rat was the central rather than the peripheral nervous system. Gildes, Castle, Gildea and Cobb [68] concluded that deficiency of vitamin B_1 alone would produce peripheral, but not funicular, degeneration of the spinal cord. Alexander, Pijoan, Myerson and Keane [101] and Alexander [102] produced hemorrhages in the brain of pigeons, in addition to the polyneuritis. In general, degeneration of the peripheral nerves, with the first and most serious disturbance in the distal portion, is a constant and most characteristic feature of human and experimental beriberi. The variations in the disturbance of the nerve roots, the sympathetic and vagal systems, the ascending fibers of the spinal cord, the ganglion cells and the vascular system seem to depend on the severity and chronicity of the disease, a possible coexistence of deficiency in other vitamins, agonal effects, the thoroughness of the pathologic studies and the type of animal used.

As discussed previously, the character and distribution of the nerve lesions in my cases fitted in extremely well with those in beriberi. However, a constant manifestation of primary irritation of the nerve cells and evidence of independent degeneration of the nerve fibers in the posterior columns and lateral tracts suggest the possibility of a concomitant deficiency in at least another vitamin, the P-P factor.

Human Pellagra.—Brierre,[135] Spessa [136] and Landouzy [137] noted hyperemia of the meninges and softenings of the spinal cord. Bouchard [71] observed hyperemia and ossification of the meninges and atrophy and softenings of the spinal cord, as well as degeneration of the posterior columns and lateral tracts and sclerosis of the spinal arteries. Verga [69] reported inflammation of the brain, ossification of the meninges and degeneration of both the white and the gray substance of the spinal cord, especially in the spinal cord in cases in which the course was rapidly fatal, and the occurrence of similar lesions of the spinal cord in cases of psychosis of nonpellagrous origin with a prolonged cachectic state. Bassi [94] recorded fatty degeneration of the cervical portion of the sympathetic system, acute hemorrhagic pachymeningitis, proliferation of the ependyma of the central canal, sclerosis of the blood vessels in the anterior horns and degeneration of the nerve tissue near the nucleus

135. Brierre, cited by Sundwall.[53]

136. Spessa, cited by Sundwall.[53]

137. Landouzy, M.: Pellagra sporadique, Bull. de l'Acad. nat. de méd. **17**:629, 1852.

of the vagus nerve. Dejerine [96] noted degeneration of the cutaneous nerves at the site of the exanthem and concluded that the cutaneous lesions in pellagra were due to trophic disturbances of the nerves. Hirsch [110] observed hyperemia and inflammation of the meninges. Tonnini [72] noted subarachnoid hemorrhages, anemia and hyperemia of the spinal cord, thickening and ossification of the meninges and degeneration of the nerve cells and the posterior and lateral tracts. De Hieronimis [109] saw proliferation of the ependyma of the central canal and foci of inflammation in the gray substance in the brain and spinal cord. Neusser [73] reported subdural hemorrhage and sclerosis of the spinal cord. Marchi [74] demonstrated degeneration of the posterior columns, the anterolateral tracts, the nerve fibers in the anterior horns and the nerve roots and pigmentary degeneration of the spinal and sympathetic ganglia. Belmondo [75] observed meningomyelitis in cases of acute involvement and degeneration of the lateral and posterior tracts, pigmentary atrophy of the anterior horn cells and thickening of the blood vessels in cases of chronic disturbance. Tuczek [56] interpreted the hyperemia, anemia, edema, hyperplasia and ossification of the meninges, obliteration of the central canal, arteriosclerosis and pigmentary change of the nerve cells as the noncharacteristic features and the sclerosis either of the posterior columns alone or of both the posterior and the lateral tracts, accompanied by degeneration of the anterior horn cells and the nerve roots, as the typical features. Gaucher and Sergent [77] mentioned the existence of fatty degeneration of the cortical nerve cells and sclerosis of the lateral tracts. Lombroso [76] concluded that the leptomeningitis and softenings of the spinal cord were constant changes, although he often noted sclerosis of the lateral and posterior tracts, involvement of the posterior nerve roots and diffuse fatty degeneration of both the sensorimotor and the autonomic nervous system. Marinesco [138] described diffuse chromatolytic changes of the nerve cells in the entire central nervous system but observed no alteration in the white substance of the spinal cord. Schreiber [139] saw anemia and edema of the meninges, brain and spinal cord, with softenings in the last two structures. Righetti [140] noted wallerian degeneration of the peripheral nerves. Grimaldi [141] and White and Taylor [142] did not observe any characteristic changes. Sandwith [61] reported that Batten had found degeneration of the posterior columns to be of root origin. Sergent [105]

138. Marinesco, M. G.: Lésions des centres nerveux dans la pellagre, Compt. rend. Soc. de biol. **51**:919, 1899.

139. Schreiber, S. H.: Ueber Pellagra, Wien. med. Wchnschr. **49**:454, 1899.

140. Righetti, cited by Kozowsky.[35]

141. Grimaldi, cited by Kozowsky.[35]

142. White, E. B., and Taylor, A. L.: A Case of Pellagra, J. Ment. Sc. **78**: 929, 1932.

and Zartarian [106] suspected the hypoplasia of the blood vessels to be a constitutional anomaly in the pellagrin, from which the pigmentary and fatty degeneration of the tissue had resulted. Babes and Sion [29] noted changes in the Betz cells, increase of pigments in the nerve cells of the entire central nervous system and degeneration of the posterior nerve roots and the posterior columns. Carmao [143] observed ossification of the subarachnoid and amyloid bodies and gliosis of the spinal cord and fatty degeneration of the nerve cells. Brugia [95] described thickening of the blood vessels, hyperplasia of the meninges and pigmentary atrophy of the nerve cells in the sympathetic ganglia. Parhon and Papinian [30] demonstrated primary irritation of the large motor nerve cells, the neurofibrils of which were either absent or displaced. Sereni [78] found sclerosis of both the lateral and the posterior columns. Gregor [31] in the cases of severe involvement observed damage of the anterior and posterior nerve roots and the peripheral nerves, in addition to occasional hemorrhages in the gray substance of the spinal cord, degeneration of the posterior, lateral and anterior tracts and primary irritation of the large motor nerve cells. Lukács and Fabinyi [32] observed degeneration of the fasciculus gracilis secondary to that of the nerve cells in the posterior horns and primary irritation of the large motor nerve cells. The Pellagra Commission of the State of Illinois [33] placed emphasis on the presence of primary irritation of the Betz cells, the anterior horn cells and the cells in Clarke's columns. Anderson and Spiller [34] demonstrated thickening of the pia and blood vessels, diffuse Marchi degeneration of the spinal cord, proliferation of the capsular cells, degeneration of the nerve cells in the spinal ganglia and primary irritation of the large motor nerve cells with intact nerve roots. Kozowsky [35] observed degeneration of the posterior and lateral columns and the anterior and posterior nerve roots, a diffuse change in the nerve cells, including primary irritation of the large pyramidal cells, and hyalinization of the small blood vessels. He called the vascular change a fundamental pathologic process and interpreted the degeneration of the spinal funiculi as a phenomenon secondary to the lesions in the precentral gyrus and the posterior nerve roots. Rezza [36] observed progressive and regressive changes of the pia, fatty degeneration of the vessel walls, diffuse involvement of the nerve cells, including primary irritation of the Betz cells and the anterior horn cells, and progressive and regressive alteration of the glia, but no systematic degeneration of the fiber tracts. Paussie [104] described hyperemia and hyperplasia of the meninges, premature arteriosclerosis and fatty degeneration of the nerve cells. Mott [37] noted fresh degeneration of the peripheral nerves, the nerve roots and the entire white substance of the spinal ganglia, anterior horns, brain stem and precentral gyrus.

143. Carmao, cited by Kozowsky.[35]

Singer and Pollock [38] observed in cases of acute involvement primary irritation of the nerve cells, proliferation of the glia and a moderate amount of perivascular infiltration and in cases of chronic disturbance fatty and fibrinoid degeneration, chronic Nissl changes of the nerve cells, increase of the glia fibers, regressive changes of the glia cells, permanent destruction of the nerve fibers, marked increase in the amyloid bodies and an occasional chronic vascular change. The primary irritation was shown by the nerve cells in the cerebral cortex, the basal ganglia, the brain stem, the cerebellar nuclei, the gray substance of the spinal cord, the spinal and sympathetic ganglia and the ganglia of Auerbach's and Meissner's plexuses in the intestine. They pointed out that this type of cell change was constantly observed in the cases of recent origin but not in those of chronic involvement. Roberts [87] reported degeneration of the pyramidal tracts and the posterior columns, occasional involvement of the posterior nerve roots and changes of the nerve cells in the spinal cord. Murlin [144] emphasized that the most vulnerable point of the attack was at the cervical region of the spinal cord. Sundwall [53] noted sclerosis of both the posterior and the lateral tracts. Pierce [40] saw slight infiltration of the meninges, thickening of the blood vessels and primary irritation of the Betz cells and the cells in the gray substance of the spinal cord. Ostertag [42] revealed that in cases of acute disturbance there was primary irritation of the Betz cells and the nerve cells in the anterior horns and the vegetative nuclei in the brain stem but no change of the nerve fibers anywhere in the nervous system. Denton [41] observed early arteriosclerosis, indefinite degenerative changes of the nerve cells and primary irritation of the large motor nerve cells in the cortex and cord but no change in the nerve fibers. Susman [145] noted congestion of the meninges and unilateral degeneration of the dorsal spinocerebellar tract. Winkelman [43] pointed out a triad of changes, namely, hyaline degeneration of the capillaries and precapillaries, diffuse fatty change of the nerve cells, glia and endothelium of the blood vessels and primary irritation of the Betz cells and the anterior horn cells. He noted only once the presence of sclerosis of the posterior columns, in which one of the posterior nerve roots was damaged. Besides the triad of changes mentioned by Winkelman, Pentschew [44] frequently observed sclerosis of the posterior and lateral tracts. Klauder and Winkelman [45] noted as a constant feature primary irritation of the large motor nerve cells. Harris [107] described hyaline changes of the capillaries and precapillaries in almost

144. Murlin, J. R.: The Amino Acid Fractions and Hippuric Acid in the Urine of Pellagrins, Hygiene Laboratory Bulletin 116, United States Treasury Department, Public Health Service, 1920, p. 45.

145. Susman, W.: The Morbid Anatomy and Histology of Pellagra, Edinburgh M. J. **33**:58, 1926.

all the organs. Langworthy [47] observed fatty degeneration of the nerve cells of the whole nervous system, sclerosis of the spinocerebellar and pyramidal tracts and damage of the nerve trunks and nerve roots in the cauda equina. Orton and Bender [19] noted chronic degenerative changes of the lateral horns and the corresponding nerve fibers. De Morsier and Starobinski [108] observed hyaline changes of the cerebral blood vessels and degeneration of the fiber tracts in the medulla oblongata. Beyer [48] confirmed the observation of Winkelman but noted no tract degeneration. Nauck [111] reported the presence of hyperplasia of the pia, edema of the brain, diffuse changes of the ganglion cells and degeneration of the spinal tracts. The observation of Marinescu was about the same as that of Pentschew, but he found, in addition, degeneration of the nerve roots and the peripheral nerves. In his series of 30 cases primary irritation of the Betz cells was a constant feature. Guillain, Bertrand, Mollaret and Lereboullet [79] described primary irritation of the motor nerve cells, hyaline degeneration of the small blood vessels and sclerosis of the posterior and lateral tracts. Rosentoul [97] described changes in the nerve fibers of the skin in cases of early pellagra. Tucker [62] noted sclerosis of the posterior columns and degeneration of the nerve cells in the spinal cord and spinal sympathetic ganglia. Bumke and Kraft [50] commented that in pellagra a pronounced change could take place in the whole nervous system; the degeneration of the spinal tracts might be not a regular manifestation, but primary irritation of the Betz cells and the anterior horn cells was a constant pathologic feature. Eddy and Dalldorf [27] reported that the characteristic lesions consisted of primary irritation of the pyramidal cells of the cerebral cortex and degeneration of the posterior and lateral tracts, whereas the involvement of the nerve roots and the peripheral nerves was rather infrequent. Stepp [51] expressed the opinion that primary irritation of the cerebral nerve cells, hyaline degeneration of the blood vessels and sclerosis of the posterior and lateral tracts were the important changes. Greenfield and Holmes [52] observed primary irritation of the Betz cells and the nerve cells in the anterior horns of the lumbar region, diffuse chromatolysis of the nerve cells throughout the entire brain, degeneration to a pronounced degree, in the fasciculus gracilis, to a less degree in the direct spinocerebellar tracts and to a slight degree in the crossed and uncrossed pyramidal tracts, disturbance of the posterior nerve roots at all levels, but most severe in the lumbar region, and some degeneration of the anterior nerve roots. These changes were striking in Nissl and Marchi preparations but were not remarkable in Weigert-Pal and scarlet red stains.

Experimental Deficiency in the P-P Factor.—Sundwall [53] observed changes in the spinal cord similar to those in human pellagra. Gildea, Wattwinkel and Castle [80] noted diffuse irregular loss of the myelin in

the white substance of the spinal cord, which, according to them, closely resembled what has been encountered in human combined system disease. Lillie [146] demonstrated degeneration of the myelin sheaths of the nerves of the lip. Crane-Lillie and Rhoads [54] and Zimmerman and Burack [65] reported degeneration of the peripheral nerves, primary irritation of the nerve cells and sclerosis of the posterior and central nerve tracts. Zimmerman, Cowgill, Bunnell and Daun [66] described degeneration of the posterior columns in 3 dogs, 2 of which showed also demyelination of the peripheral nerves and the third degeneration of the peripheral nerves without any changes in the cord. Gildea, Castle, Gildea and Cobb [68] observed degeneration of the cerebral nerve cells and Purkinje cells, fat in the nerve cells and the perivascular spaces in the cerebral cortex and definite myelin lesions of the spinal cord in 7 dogs and peripheral neuritis in 3 dogs. Zimmerman, Cowgill and Fox [67] observed peripheral neuritis, which was most pronounced in the distal portions of the nerves in the hindlimbs, degeneration of the posterior and anterior nerve roots and sclerosis of the posterior columns but no disturbance of the nerve cells or demyelination of the pyramidal tracts.

Pathogenetic Factors.—In general, primary irritation of the nerve cells is a regular pathologic manifestation in human pellagra, which has been observed occasionally also in animals deficient in the P-P factor. The variations in involvement of the spinal tracts, nerve roots, peripheral nerves and blood vessels seem to be related to the same factors as those mentioned in the case of beriberi. The nerve lesions in the present cases presented enough features to establish the pathologic picture as characteristic of both beriberi and pellagra, i. e., a deficiency of the vitamin B complex.

Although the pathologic process in beriberi may resemble closely that in pellagra, the distribution and the order of frequency of the lesions in the one condition are more or less the reverse of the those in the other. In beriberi the peripheral nerves are the primary site of damage, while in pellagra the brain seems to be the early focus of disturbance. As the disease progresses further the process of degeneration extends centripetally in beriberi and centrifugally in pellagra.

In a report on the selective affinity of the vitamins for certain parts or pathways of the nervous system, Wechsler [147] assumed that despite the fact that the fibers seemed to be similar in various tracts, apparently some chemical difference caused a selective response to the presence of various drugs, toxins, viruses, proteins and food. Tuczek [56] commented

146. Lillie, R. D.: Pathology of Experimental Blacktongue, National Institute of Health Bulletin 162, United States Treasury Department, Public Health Service, 1933, p. 13.

147. Wechsler, in discussion on Zimmerman, Cowgill and Fox.[67]

that the fiber systems differ from each other in their embryonic development, chemical structure and resistance to a chemical noxus. The long tracts are the last to be provided with myelin sheaths and therefore show the least resistance to damage. Sundwall applied the exhaustion theory of Edinger to account for the selective involvement of the tracts of the cord. The higher the functional demands made on the nerve cells, the more likely are they to suffer from exhaustion. The pyramidal tracts and the reflex arc fibers, especially the sensory components, function most in the normal activities of life and hence are the first to show the results of exhaustion in malnutrition and intoxication.

It is beyond the scope of the present report to review the theories concerned with the etiology of beriberi and pellagra; suffice it to say that the validity of the theory of vitamin deficiency has been proved for beriberi through the studies of Eijkman,[120] Yamagiwa,[103] Königer,[148] van Dieren, Hose and others,[149] Fletcher,[150] Braddon,[151] Shiga and Kusama,[121] Andrews,[122] Vedder,[152] Schaumann,[125] Strong and Crowell,[153] Vedder and Clark,[129] Kimura,[130] Voegtlin and Lake,[123] Findlay,[92] McCarrison,[93] Fraser and Stanton,[124] Hofmeister,[98] Kingery and Kingery,[126] Woolard,[132] Culley,[133] Tsunoda and Kura,[134] Zimmerman and Burack,[65] Gildea, Castle, Gildea and Cobb,[68] Alexander and his associates,[101] Williams and Spies,[119] Funk,[154] and Jansen and Donath,[155] for pellagra through the investigations of Harris,[156] Goldberger and Wheeler,[157] Spies, Cooper and Blankenhorn,[158] Spies, Aring, Gelperin and Bean [159] and Spies, Bean and Stone.[160] However, we do not know

148. Königer, cited by Dürck.[24]

149. van Dieren, Hose and others, cited by Dürck.[24]

150. Fletcher, W. L.: Rice and Beriberi, J. Trop. Med. & Hyg. **12**:127, 1909.

151. Braddon, L.: The Etiology of Beriberi, Brit. M. J. **1**:1007, 1909.

152. Vedder, E. B.: A Fourth Contribution to the Etiology of Beriberi, Philippine J. Sc., Sect. B **7**:415, 1912.

153. Strong, R. P., and Crowell, B. C.: The Etiology of Beriberi, Philippine J. Sc., Sect. B **7**:271, 1912.

154. Funk, cited by Schüffner.[58]

155. Jansen and Donath, cited by Schüffner.[58]

156. Harris, H. F.: Pellagra, New York, The Macmillan Company, 1919.

157. Goldberger, J., and Wheeler, G. A.: Experimental Pellagra in White Male Convicts, Arch. Int. Med. **25**:451 (May) 1920.

158. Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, J. A. M. A. **110**:622 (Feb. 26) 1938.

159. Spies, T. D.; Aring, C. D.; Gelperin, J., and Bean, W. B.: The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid, Am. J. M. Sc. **196**:461, 1938.

160. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate with Special Reference to the Vasomotor Action and the Effect on Mental Symptoms, J. A. M. A. **111**:584 (Aug. 13) 1938.

fully as yet the exact effect of vitamin B_1 and the P-P factor on cellular metabolism. A purely morphologic study of the nervous system would yield little information as to the mode of action on the nerve tissue of the various factors of the vitamin B complex.

With reference to the mechanism of avitaminosis in my cases, it is necessary to consider in particular the roles played by the lesions of the intestine, the disseminated tuberculosis of various organs and the malnutrition.

In human beings, at least, three factors operate to produce a dietary deficiency: an inadequate intake of the essential food elements, which is responsible for the so-called primary deficiencies; a faulty absorption or an excessive loss as a result of altered function of the gastrointestinal tract, and an increased demand resulting from some interference with storage or some failure of utilization by the cells, which may be responsible for the so-called secondary deficiencies. Each of these factors alone is sufficient to give rise to avitaminosis. In view of the fact that avitaminosis itself can produce changes in the gastrointestinal tract (Dürck,[24] McCarrison,[93] Cramer,[161] Goldblatt and Benischek,[162] Pillat,[163] Cannon,[26] Tilden and Miller,[164] Moore and Plymate,[165] Marks,[166] Brown,[167] Hare,[168] Webster and Armour,[169] Zimmerman, Cowgill, Bunnell and Daun,[66] Mackie and Pound,[170] Eddy and Dalldorf,[27] Herzenberg,[171] Williams and Spies,[119] Schüffner [58] and Ceelen [172]) and that avitaminosis is not infrequently complicated by diseases which cause a

161. Cramer, W.: On the Mode of Action of Vitamins, Lancet **1**:1046, 1923.

162. Goldblatt, H., and Benischek, M.: Vitamin A Deficiency and Metaplasia, J. Exper. Med. **46**:699, 1927.

163. Pillat, A.: The General Symptoms of Keratomalacia of Adults, Chinese M. J. **43**:907, 1929.

164. Tilden, E. B., and Miller, E. G.: The Response of the Monkey (Macacus Rhesus) to Withdrawal of Vitamin A from the Diet, J. Nutrition **3**:121, 1930.

165. Moore, C. U., and Plymate, H. B.: Studies in the B Vitamins: VI. Further Consideration of Pyloric Obstruction in Rats, Am. J. Physiol. **102**:605, 1932.

166. Marks, H. E.: Chronic Vitamin B Deficiency: A Clinical Study, M. J. & Rec. **135**:231, 1932.

167. Brown, M. R.: The Pathology of the Gastrointestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord, New England J. Med. **210**:473, 1934.

168. Hare, D. C.: Nonspecific Colitis in Relation to Deficiency Diseases and Anemia, Brit. M. J. **2**:162, 1934.

169. Webster, D. R., and Armour, J. C.: Vitamin B Complex and Gastric Secretion, Proc. Soc. Exper. Biol. & Med. **31**:463, 1934.

170. Mackie, T. T., and Pound, R. E.: Changes in the Gastrointestinal Tract in Deficiency States, J. A. M. A. **104**:613 (Feb. 23) 1935.

171. Herzenberg, cited by Eddy and Dalldorf.[27]

172. Ceelen, cited by Mollow.[192]

further inadequacy in the vitamin metabolism and thus establish a vicious cycle harmful to the patient, it is usually possible to find more than one such factor operating in the same person, and therefore it is difficult to separate sharply the primary from the secondary deficiencies. In my cases all three of these factors seemed to operate, though probably not to an equal degree. There are good reasons to suspect that the diet in the Red Cross base hospital in question was poor (Wu and Wu [173]) and that these patients, as well as the other soldiers, suffered from subclinical avitaminosis. As a result of tuberculosis and profuse diarrhea, these patients probably also suffered from impaired appetite due to increased demand for vitamins not supplied and insufficient intake of vitamins lost partly because of diarrhea and partly because of inadequate assimilation. Therefore an endemic avitaminosis, chiefly secondary, broke out. Avitaminosis manifested in the form of polyneuritis, spinal funicular disease or pellagra occurs frequently after disturbances of the gastrointestinal tract or febrile disease (Dürck,[24] Müller-Dehan,[174] Schlesinger,[175] Willcox,[176] Rolph,[177] Bryan,[178] Murlin,[144] Coyan and Debray,[179] Modes,[180] Nuzum,[181] Bender,[182] O'Leary,[63] Elliot,[183] Turner,[184] Keefer, Huang and Yang,[2] Yang and Hu,[3] Wechsler,[185] Langworthy,[47] Komeda,[186]

173. Wu, H., and Wu, D. Y.: Study of Dietaries in Peking, Chinese J. Physiol. (rep. ser.), 1928, no. 1, p. 135.

174. von Müller-Dehan, A.: Beobachtungen zur Klinik und Therapie der Dysenterie, insbesondere der post-dysenterischen und post-ulcerösen Polyneuritis, Wien. med. Wchnschr. **65**:653, 1915.

175. Schlesinger, H.: Dysenterische Polyneuritis bei Kriegsteilnehmern, Med. Klin. **11**:383, 1915.

176. Willcox, W. H.: Beriberi, with Special Reference to Prophylaxis and Treatment, Lancet **1**:553, 1916.

177. Rolph, F. W.: Cancer of the Stomach and Pellagra in the Same Patient, Canad. M. A. J. **6**:323, 1916.

178. Bryan, R. C.: Cancer of Stomach with Associated Pellagra, Virginia M. Monthly **46**:107, 1919.

179. Coyan, A., and Debray, J.: Polynévrite consécutive à une dysentérie bacillaire à Shiga, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:129, 1922.

180. Modes, U.: Zur Etiologie der funikulären Spinalerkrankung, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:291, 1922.

181. Nuzum, F. R.: Pellagra Associated with Annular Carcinoma of the Terminal Portion of Ileum, J. A. M. A. **85**:1861 (Dec. 12) 1925.

182. Bender, W. L.: Pellagra Secondary to Lesions of the Stomach Interfering with Nutrition, J. A. M. A. **84**:1250 (April 25) 1925.

183. Elliot, A. R.: Pellagra Secondary to Carcinoma of the Colon, M. Clin. North America **11**:237, 1927.

184. Turner, R. H.: Pellagra Associated with Organic Disease of the Gastrointestinal Tract, Am. J. Trop. Med. **9**:129, 1929.

185. Wechsler, I. S.: Unrecognized Cases of Deficiency Polyneuritis (Avitaminosis?), M. J. & Rec. **131**:441, 1930.

186. Komeda, M.: Clinical and Experimental Studies on Influence of Dysentery Toxin upon Nervous System, Orient. J. Dis. Infants **11**:33, 1932.

Eustermann and O'Leary,[64] Menzel,[187] Thaysen,[188] Yang and Huang,[7] Alexander and Wu,[6] Flinker,[189] the Stubbe-Teglbjaergs,[190] Brown,[167] Holme,[191] Mollow [192] and Stepp [51]).

In his discussion of the effect of the dysentery toxin on the human nerve tissue, Spatz [193] described diffuse changes of the ganglion cells and occasional foci of devastation in the superficial layer of the cerebral cortex; Oesterlin [194] noted edema, meningeal hemorrhage and glial proliferation in the cerebellar cortex; Spielmeyer [195] observed annular hemorrhages and foci of destruction of vascular origin in the brain; Scherer [196] reported annular hemorrhages and lobular atrophy of the cerebellum, and Alexander and Wu observed degeneration of the ganglion cells, including soaking changes of the neurofibrils and progressive alteration of the glia. However, these changes might not signify a direct effect of the dysentery toxin. On the contrary, they might be preagonal, due to hydration (Alexander and Wu [6]) and perhaps also to a deficiency in vitamins B_1 and C. The experimental work with the dysentery toxin of Dopter,[197] Karasawa,[198] Lotmar [199] and Tupa [200] has shown a degenerative-productive process in the nervous system designated as disseminated encephalomyelitis, which is distinctly different from that in pure avitaminosis. In my cases, as in many others, such changes were not presented to support the belief of a direct effect of the dysentery toxin on the nerve tissue.

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187. Menzel, W.: Ueber zwei Fälle von bazilläre Ruhr, Deutsche Ztschr. f. Nervenh. **126**:265, 1932.

188. Thaysen, T. E. H.: Secondary Pellagra, Acta med. Scandinav. **78**:513, 1932.

189. Flinker, R.: Die Aetiologie und Pathogenese der Pellagra, Wien. med. Wchnschr. **84**:930 and 960, 1934.

190. Stubbe-Teglbjaerg, E., and Stubbe-Teglbjaerg, H. P.: Sekundäre Pellagra, Centralbl. f. d. ges. Neurol. u. Psychiat. **69**:509, 1934.

191. Holme, cited by Greenfield and Holmes.[52]

192. Mollow, W.: Ueber Pellagra, in Stepp.[51]

193. Spatz, cited by Weimann, W.: Infektionen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 119.

194. Oesterlin, cited by Weimann, W.: Infektionen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 119.

195. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 401.

196. Scherer, H. J.: Beiträge zur pathologischen Anatomie des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:337, 1932.

197. Dopter, M. C.: Effects expérimentaux de la toxine dysentérique sur le système nerveux, Ann. Inst. Pasteur **19**:353, 1905.

198. Karasawa, M.: Die Wirkung des Dysenterietoxins auf das Zentralnervensystem, Ztschr. f. Immunitätsforsch. u. exper. Therap. **6**:390, 1910.

199. Lotmar, F.: Zur Wirkung des Dysenterietoxins auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:345, 1912.

200. Tupa, A.: Contribution à l'étude des lésions du système nerveux central, provoquées par le toxine dysentérique, Compt. rend. Soc. de biol. **92**:1141, 1925.

The existence of tuberculosis of one or more organs in the present cases emphasizes its prevalence in China, especially among the poorer class of people. The role played by tuberculous infection in the field of vitamin metabolism is twofold. On the one hand, it can give rise to deficiency through poor appetite, increased demand, excessive loss or faulty absorption of the vitamins, while, on the other hand, avitaminosis seems to render the patient more susceptible to tuberculosis or to the flaring up of a preexisting focus (Langworthy [47]). Although the tuberculous infection in my cases was disseminated, in none did the nerve tissue show such a disturbance. Therefore the nerve lesions in these cases could not be related directly to the tuberculosis.

Despite the fact that the pathologic changes in the nervous system of the animals suffering from inanition are essentially the same as the changes in those deprived of vitamin B_1 or of both vitamin B_1 and the P-P factor (Davison and Stone [201]), it is inconceivable that in the human cases starvation would exist without deficiency in the vitamins, though a reverse situation is possible. Therefore the factor of inanition quite likely played an etiologic role in the present cases.

Except in 1 instance, no pellagrous lesions of the skin were observed in the present series. Whereas the word pellagra means "rough skin" and the cutaneous lesion is considered by most authors as a pathognomonic sign of pellagra, there have been cases of pellagra sine pellagra, as has been mentioned by Biggam and Ghalioungui [202] and Mollow,[192] in which the gastrointestinal and the nervous disturbances may make their appearance earlier than the cutaneous lesions. Kassirsky and Burova [203] pointed out that in about 24 per cent of the cases of pellagra there was no cutaneous change. Therefore the absence of a cutaneous manifestation in most of my cases does not speak against the diagnosis of pellagra.

The occurrence of a multiple vitamin deficiency in the same person, as presented in my cases, especially in connection with the vitamin B complex, is not infrequent. Many such instances have been reported in the literature (Darling,[204] Mendelson,[205] Weech,[206] Eddy and Dalldorf,[27] Williams and Spies [119] and Schüffner [58]).

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201. Davison, C., and Stone, L.: Lesions of the Nervous System of the Rat in Vitamin B Deficiency, Arch. Path. **23**:207 (Feb.) 1937.

202. Biggam, A. G., and Ghalioungui, P.: Pellagra: Its Clinical Features and Pathology with Observations on the Treatment of Its Nervous Manifestations by Massive Doses of Iron, Lancet **2**:1198, 1933.

203. Kassirsky, J., and Burova, L.: Zur Klinik der Pellagra in Mittelasien, Arch. f. Schiffs- u. Tropen-Hyg. **36**:323, 1932.

204. Darling, S. T.: The Pathologic Affinities of Beriberi and Scurvy, J. A. M. A. **63**:1290 (Oct. 10) 1914.

205. Mendelson, R. W.: A Case of Combined Pellagra and Beriberi, J. Trop. Med. & Hyg. **26**:6, 1923.

206. Weech, A. A.: Association of Keratomalacia with Other Deficiency Diseases, Am. J. Dis. Child. **39**:1153 (June) 1930.

SUMMARY

The literature dealing with neuropathologic studies on both human and experimental deficiency of vitamin B_1 and the P-P factor is reviewed.

An endemic of so-called secondary B complex avitaminosis was encountered in a group of 13 Chinese soldiers who had suffered primarily from dysentery and tuberculosis. Besides an inadequate supply, the factors of poor absorption and an excessive loss of the vitamins also played an important role in the production of avitaminosis in these patients.

The diagnosis of beriberi and pellagra was based on the demonstration of a uniform, characteristic neuropathologic picture.

The possible histopathogenesis of the outstanding individual nerve lesions is discussed.

The neuropathologic process was degenerative and involved both the sensorimotor and the autonomic nervous system.

The neuropathy of the peripheral nerves was the anatomic substratum of beriberi, while primary irritation of the Betz cells was a constant morphologic manifestation in pellagra.

The neuropathologic process tended to proceed centripetally in beriberi and centrifugally in pellagra.

The involvement of the peripheral nerve trunks and the nerve roots was predominantly confined to the sensory fibers, their distal portions being more severely damaged than their proximal portions.

The lesions of the spinal cord were characterized by frequent sclerosis of the posterior columns, especially the fasciculus gracilis, and occasional involvement of the pyramidal and the lateral sensory tracts.

The degeneration of the ascending fibers of the spinal cord was chiefly of wallerian type secondary to a neuropathy of the posterior nerve roots. There was, however, evidence to suggest an independent process. Therefore the spinal funicular disease in the present cases was not exactly systemic.

The frequency of the funicular involvement was apparently related to the duration and the severity of the deficiency.

A typical cutaneous lesion of pellagra was noted in 1 case.

The exact mode by which the vitamins act on the nerve tissue is not known. A mere morphologic approach seemed to be futile in any attempt to solve this problem.

Further neuropathologic studies on human beriberi and pellagra should include a study of the neuromuscular end organ and the glycogen content, the mitochondria and the oxidase reaction (Dutcher [207]) of the nerve cells in selected cases.

A careful neuropsychiatric examination is indicated in cases of disturbance of the gastrointestinal tract.

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207. Dutcher, R. A.: Vitamine Studies: Observations of the Catalase Activity of Tissues in Avian Polyneuritis, J. Biol. Chem. **36**:63, 1918.

No pathologic examination in cases of lesions of the gastrointestinal tract is considered satisfactory without an adequate study of the nerve tissue.

It is necessary to supply adequate vitamins in cases of gastrointestinal trouble, especially by the parenteral route, even though no frank signs of neuropsychiatric disorder can be detected clinically.

The general pathologic examinations were performed by Drs. K. Y. Ch'in, S. T. Pai, S. T. Wu and V. T. Lieu, of the department of pathology, and the studies on the nervous system were made in the neuropathologic laboratories of the division of neurology and psychiatry of Peiping Union Medical College.

Prof. W. Scholz assisted in the study of these cases, and Mrs. Grombach helped in the staining technic in part of the neuropathologic investigations which were made during a period of study at the Deutsche Forschungsanstalt für Psychiatrie, Munich, Germany (1938-1939).

The Department of Pathology of the Peiping Union Medical College gave permission for inclusion of the general autopsy observations.

Case Reports

A COMPLICATION OF PARAVERTEBRAL INJECTION OF ALCOHOL

Report of a Case

F. J. Hirschboeck, M.D., and M. G. Gillespie, M.D., Duluth, Minn.

The attempt to control the pain of angina pectoris by injection of the sympathetic nerves is a fairly recent procedure. Mandl,[1] in 1925, according to Swetlow, was the first to use paravertebral injection of procaine for the relief of the pain of angina pectoris. In 1926 Swetlow[2] reported the use of alcohol block of the sympathetic fibers in a group of 8 patients with cardiac disease. Since then there have been several publications of small groups of cases. Levy and Moore,[3] in 1931, collected 57 cases from the literature and reported 9 cases from his personal experience. Analysis of the cases showed complete relief in 51 per cent, improvement in 34 per cent and no relief in 15 per cent. As untoward effects, the authors reported pleural effusion in 2 cases, postoperative collapse in 2 cases and bloody expectoration in 1 case. There were no deaths.

In a personal communication, dated June 23, 1939, Dr. James C. White stated that he had performed about 100 injections of alcohol without any serious complications. To prevent such complications he advised the following precautions: 1. Exert suction on the syringe after each 0.5 cc. of procaine or alcohol is injected. 2. Be particularly careful in making the first injection. 3. Always inject procaine first and observe whether there is anesthesia or weakness of the lower part of the body. 4. Finally, always insert the needle unattached to the syringe.

The possibility of serious injury from paravertebral injection of alcohol is illustrated by the report by Molitch and Wilson[4] of a case in which a Brown-Séquard syndrome followed a paravertebral injection of alcohol, with fortunate recovery. They expressed the belief that a needle entered the spinal canal through the intervertebral foramen and actually pierced the cord.

1. Mandl, cited by Swetlow, G. I.: Paravertebral Alcohol Block for the Relief of Pain, Am. J. Surg. **9**:88 (July) 1930.

2. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Am. Heart J. **1**:393 (April) 1926.

3. Levy, R. B., and Moore, R. L.: Paravertebral Injection of Alcohol for the Relief of Cardiac Pain: A Review of Experience to Date and a Report of Nine Cases, Arch. Int. Med. **48**:146 (Dec.) 1931.

4. Molitch, M., and Wilson, G.: Brown-Séquard Paralysis Following a Paravertebral Alcohol Injection for Angina Pectoris, J. A. M. A. **97**:247 (July 25) 1931.

Groff and Lewy [5] reported a case of death several months after subarachnoid injection of alcohol for the relief of angina pectoris. Complete transverse myelitis followed the injection. They concluded that alcohol should never be injected intrathecally anywhere over the spinal cord.

The following case illustrates again the disastrous complication which follows the accidental injection of alcohol either into the spinal cord or intrathecally.

REPORT OF CASE

O. N., a man aged 59, on March 22, 1939 consulted one of us (F. J. H.) because of shortness of breath, pain radiating down the left arm, especially with exertion, and slight vertigo, of about six weeks' duration. The pain and distress were severe enough to incapacitate him partially. There was no nocturnal dyspnea, no pain in the chest and no cough.

Past History.—The patient was first seen in the clinic in 1923, at the age of 42. He then complained of backache and a visual disturbance. The latter was found to be due to a refractive error. In 1934 he was again examined, because of a digestive complaint. It was found that he had hypoacidity, of questionable significance. The stomach appeared normal on fluoroscopic inspection. Roentgen examination of the gallbladder revealed nothing abnormal. In 1935 he again was seen because of the stomach complaint. A test meal at this time showed free hydrochloric acid of 24 degrees and total acidity of 32 degrees. Fluoroscopic inspection of the stomach again failed to show any significant condition. In 1936 he had gonorrheal urethritis.

Family History.—The patient's father died at the age of 58 of a "carbuncle." The mother died at the age of 65, the cause being unknown. Two sisters had died, 1 at 55 and the other at 25 years of age. Two brothers and 1 sister were reported to be living and well.

Marital History.—His wife and 3 children were living and well.

Examination.—The patient was tall and fairly well nourished. The mouth and throat were normal. There was no evidence of goiter. The heart and lungs were reported to be normal. The blood pressure was 112 systolic and 80 diastolic. The electrocardiogram showed a slight arborization defect. Examination of the abdomen, extremities and back revealed nothing of significance. The knee jerks were normal. The hemoglobin content was 13.5 mg. per hundred cubic centimeters. Urinalysis revealed normal constituents.

Treatment.—Between March 22 and June 2, 1939 the patient was treated with theophylline with ethylene diamine U. S. P., phenobarbital and bromides, on the assumption that he was suffering from disease of the coronary vessels with angina. His activities were curtailed. However, since there was no improvement, hospitalization was advised.

He was admitted to the hospital on June 2 for a paravertebral injection of alcohol. On June 5 the injection was carried out according to the method of Labat. Needles were inserted in the interspaces between the first and the fifth thoracic spine on the left side, and 4 cc. of a 1 per cent solution of procaine hydrochloride and 2 cc. of absolute alcohol were injected through each needle. There was no reaction to the procedure.

Because there was no relief, the procedure was repeated on June 8. When the needle was inserted in the space opposite the fifth thoracic spine, the patient complained of rather severe pain "around toward his stomach." Five cubic centi-

5. Groff, R. A., and Lewy, F. H.: Danger of Subarachnoid Injection of Alcohol for Relief of Pain, Arch. Neurol. & Psychiat. **45**:533 (March) 1941.

meters of a 1 per cent solution of procaine hydrochloride and 2 cc. of absolute alcohol were injected through the needles. It was the belief of one of us (M. G. G.) that the fluid had been injected either into or close to the fifth thoracic intercostal nerve after it left the vertebral foramen. After the procedure was finished, the patient complained of numbness of the left arm and the lower extremities and of inability to move the lower extremities. Four hours later he was able to move the right leg. Nine hours later he complained of pain in the left side of the abdomen and the left leg. His temperature rose to 102 F. It was evident that he had a Brown-Séquard syndrome.

Course.—A neurologic examination two days after the operation revealed the following changes: The pupils were small, the right being slightly irregular and a little larger than the left. Both reacted slightly to light. The eyegrounds were normal. Moderate arcus senilis were present. The cranial nerves were normal. There were loss of motor power of the left leg and sensory loss on the right side, extending to the seventh thoracic level. Reflexes were present on the upper right side of the abdomen. Those on the left side were absent. A Babinski sign was present bilaterally.

On June 10 the abdomen was distended, and the patient complained of inability to void and difficulty in expelling enemas. On June 12 he had acute conjunctivitis on the left side and herpes labialis. On July 30, seven weeks after operation, he had slight voluntary motion of the toes of the left foot. Sensation in this extremity was more acute than normal. On July 14 he began to void voluntarily, and on July 16 voluntary motion in the left ankle had returned. Sensation on the right side was still absent. His temperature at this time was normal.

Treatment included administration of thiamine hydrochloride and physical therapy. He was able to leave the hospital on July 31. A regimen of massage and active and passive motion was diligently carried out in the weeks that followed. By August he was able to be up and in a wheel chair.

In February 1940 he was able to void and to get about with the aid of crutches. Neurologic examination at this time revealed anesthesia to pain on the right side up to the level of the greater trochanter and relative anesthesia to the level of the umbilicus. The knee jerks were increased over the normal bilaterally. A Babinski sign was present on both sides, being more evident on the left.

A brace was ordered to stabilize the left hip and knee joint.

On July 11, 1940, thirteen months after the injection, neurologic examination revealed that he had all component motions in the left leg but had difficulty in stabilizing himself on standing and walking. Dissociation of sensation was present on the right side up to the crest of the ilium.

SUMMARY

Paravertebral injection of alcohol for the relief of anginal pain may be followed by severe injury to the spinal cord.

To prevent complications, the precautions outlined by Dr. White, especially suction on the syringe to make certain the needle is not in the spinal canal and observation of the sensory and motor functions of the lower extremities after injection of the procaine solution, should be adhered to.

Three cases illustrating serious injury to the cord following this procedure are cited; 2 from the literature are referred to briefly and 1, from our personal experience, is described in detail.

205 West Second Street.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

STATE OF MOTOR CENTERS IN CIRCULATORY INSUFFICIENCY. ERNEST SIMONSON and NORBERT ENGER, Arch. Int. Med. **68**:48 (Sept.) 1941.

The fusion frequency of flicker was previously reported as being decreased in circulatory insufficiency. This decrease is probably due to a reduced oxygen supply to the central nervous system. The effect of fatigue on the motor centers has much practical significance and its measurement is important, since performance is the objective clinical evidence of fatigue.

The test is performed by having the subject stand in front of a table on which an impulse counter is placed. The patient touches the button of the counter with his middle finger as fast as possible for a minute. The values which seemed especially important are the maximum frequency, the minimum frequency and the difference between the maximum and the minimum frequency. After a minute's pause the test was repeated in order to investigate the possible influence of adaptation.

BECK, Buffalo.

CHANGES IN BRAIN VOLUME DURING ANESTHESIA: THE EFFECTS OF ANOXIA AND HYPERCAPNIA. J. C. WHITE, M. VERLOT, B. SELVERSTONE and H. K. BEECHER, Arch. Surg. **44**:1 (Jan.) 1942.

Experiments were designed to study the factors responsible for swelling of the brain during the course of intracranial operations. Adult cats were used. The degree of cerebral swelling was measured by the determination of the differential ratio of brain volume to cranial capacity, using a modified method which permitted accurate measurements in the small head of the cat. In unanesthetized animals the differential index averaged 10.5 per cent. With light pentobarbital sodium or ether anesthesia no significant change occurred. When the anesthetized animal breathed oxygen-nitrogen mixtures containing less than 13 per cent oxygen the differential index dropped to an average of 6.5 per cent. Under nitrous oxide anesthesia swelling of the brain occurred which closely resembled that in the anoxic animals. Cats breathing 30 per cent oxygen and 5 to 10 per cent carbon dioxide had normal differential ratios.

The residual volume of blood in the brain was determined in all experiments to show that cerebrovascular engorgement was not responsible for the diminution of the differential index of brain volume. Measurements of the cisternal pressure failed to show any correlation between the degree of swelling and the cerebrospinal fluid pressure. In the majority of animals the final pressures were low. The authors believe that during prolonged periods of anoxia the volume of cerebrospinal fluid is reduced. They conclude that anoxia results in an increase of intracellular or extracellular fluid or both.

GRANT, Philadelphia.

THE CHARACTER AND QUALITY OF SENSORY LOSS FROM DEAFFERENTATION OF DERMATOMES IN MAN. RUPERT B. RANEY, Bull. Los Angeles Neurol. Soc. **6**:55 (June) 1941.

Raney studied the sensory losses in 21 cases in which posterior rhizotomy had been done for various therapeutic purposes, chiefly in the lumbosacral region. Both the motor and the sensory roots were sectioned in 2 cases. All the nerves sectioned were identified by determining the spinal foramens through which they made their exist. Carefully measured stimuli were used in estimating the degree of sensory loss.

Raney discovered that the "older" sensations were more strictly confined to the sectioned dermatomes, while the "more recently acquired" sensations showed considerable overlapping. The only exception was in the cervical region, where overlapping was less marked. Raney discovered that while Foerster was correct in stating that complete anesthesia practically never occurred after section of a single root, some sensory loss always resulted. His observations showed that after section of a single sensory root pain sensibility was almost completely abolished in the corresponding dermatome. Temperature sensibility was less extensively diminished than pain because of the greater overlapping from adjacent dermatomes, while in the marginal zones only one type of temperature (heat or cold) was ordinarily recognized. Tactile sensation generally showed no change or a slight decrease in the dermatome in question, while vibratory sensation was more severely affected. The sense of pressure showed little or no loss unless three consecutive roots were sectioned. When one or two roots were sectioned bilaterally, the resulting disturbance was often one of sensory dissociation; there was marked impairment of pain and temperature sensation and but little disturbance of other modalities. In addition, bilateral root sections often revealed inequality and asymmetry between the dermatomes on the two sides.

MACKAY, Chicago.

CARBOHYDRATE METABOLISM IN THIAMINE DEFICIENCY. H. A. HARPER, J. Biol. Chem. **142**:239, 1942.

The relation of vitamin B_1 to carbohydrate metabolism was one of the earliest observed functions of a vitamin. The problem has been more or less continuously investigated up to the present time, and most of the evidence indicates that in vitamin B_1 deficiency there are some interference with glycogen storage, hyperglycemia and characteristic errors in carbohydrate metabolism. Ever since the discovery of the role of thiamine as a constituent of cocarboxylase and its consequent effect on pyruvate oxidation, studies in vitro of cellular metabolism in thiamine deficiency have indicated that a rather generalized disturbance of carbohydrate metabolism exists.

Certain aspects of carbohydrate metabolism in vivo were studied by Harper in animals reduced to a subacute state of thiamine deficiency. When such animals were compared with normal ones, there was observed a decrease in the rate of absorption of dextrose from the intestine and the extent of hepatic glycogenolysis. This subacute state of thiamine deficiency did not alter the ability of the animal to convert orally administered *l* (+)-sodium lactate or sodium pyruvate into hepatic glycogen.

In the thiamine-deficient animals, dextrose was superior as a ketolytic agent for the reduction of an endogenous ketonuria produced by high fat diets.

PAGE, Indianapolis.

THE METABOLISM OF VITAMIN B_6. J. V. SCUDI, R. P. BUHS and D. B. HOOD, J. Biol. Chem. **142**:323, 1942.

The authors present evidence to show that both man and the dog excrete large amounts of ingested vitamin B_6 in the urine in the form of a conjugate, whereas the rat does not. This conjugate involves the 3-hydroxyl group of the vitamin and is probably a glucuronide or an ethereal sulfate. Concentrations of this material can be quantitatively measured by the indophenol reaction following hydrolysis.

A second excretion product has also been detected in the urine of man and the dog, and to a lesser extent in that of the rat. This product is conjugated by man and the dog but not by the rat. The structure of this metabolite has been considered, and it has been shown that the 4-hydroxymethyl group of the vitamin is altered to produce this compound. The metabolite can be quantitatively measured by the indophenol reaction carried out with a borate buffer. The excretion of unchanged vitamin B_6 in the dog has been confirmed by isolation.

PAGE, Indianapolis.

ELECTROKINETIC CHANGES IN THE ENDOLYMPH AS A HYPOTHETICAL CAUSE OF FALLING AND PAST-POINTING DUE TO STIMULATION BY GALVANIC CURRENT. LEWIS J. POLLOCK, ISIDORE FINKELMAN and I. C. SHERMAN, J. Nerv. & Ment. Dis. **93**:473 (April) 1941.

Although it has been known for a long time that the passage of an electric current through the head produces vertigo and a tendency of the subject to fall and past point toward the anode, controversy still exists as to the point and manner of action of the current. Pollock and his associates point out that it is unlikely that the current stimulates the vestibular nerve directly because these reactions do not occur on application of an alternating current such as is effective in stimulating other nerves in the body and because the calculated chronaxia of the falling reaction is much greater than that of other nerves. In addition, the falling reaction occurs only on the continuous passage of current and not on make or break. In a new series of experiments Pollock and his associates confirmed these facts and discovered further that a unidirectional pulsating current with a frequency of 15,000 per second caused past pointing toward the anode. Such a current produces stimuli with a duration of only three hundred-thousandths second, suggesting a degree of irritability unlikely in the vestibular nerve. They concluded, therefore, that the passage of a current through the head does not stimulate the vestibular nerve directly but produces some physical change in the endolymph. That this change is not the localized production of heat or electrolysis is suggested by the fact that the average amperage of a pulsating current required to produce falling and past pointing varied with the duration of the individual pulsations. On the other hand, the relations of current, duration of stimuli and interval between stimuli found in the production of falling or past pointing are the same as those described for an electrophoretic displacement of solid, liquid or gaseous particles in a fluid medium. This fact suggests to the authors that an electric current passing through the head produces vertigo, falling and past pointing by inducing such an electrokinetic change in the endolymph and not by stimulating the vestibular nerve.

MACKAY, Chicago.

ISOLATION OF INTRINSIC AND MOTOR MECHANISM OF THE MONKEY'S SPINAL CORD. S. TOWER, D. BODIAN and H. A. HOWE, J. Neurophysiol. **4**:388 (July) 1941.

This brief study demonstrates the feasibility of isolating regions of mature spinal cord from all ingoing nerve impulses and utilizing them for examination of various questions in neuroanatomy and neurophysiology. It has given a picture of the intrinsic and motor mechanism of the spinal cord cleared of posterior root and descending fibers, showing the magnitude, variety and arrangement of the intrinsic system in the monkey. Finally, it has confirmed the conclusion, reached after a much longer study of isolated segments in dogs, that the mechanism in the mammalian cord operates only under the stimulus of arriving nerve impulses. Deprived of such excitation the cord produces no activity which reaches effectiveness in the skeletal musculature.

ALPERS, Philadelphia.

FIBRILLATION IN SKELETAL MUSCLE IN RELATION TO DENERVATION AND TO INACTIVATION WITHOUT DENERVATION. S. TOWER, H. A. HOWE and D. BODIAN, J. Neurophysiol. **4**:398 (July) 1941.

To investigate the possibility that surgical isolation of the spinal cord from all ingoing nerve impulses might constitute a functional denervation of the dependent skeletal muscle such that this enters into fibrillation, the lumbosacral region of the cord was so isolated in 2 monkeys and, in addition, one sciatic nerve was cut in each. Two weeks thereafter leg muscles were exposed on the two sides and examined for fibrillation. Muscle still in possession of its innervation was found to be at rest, not fibrillating, but muscle denervated either by sciatic section or, in 1 animal, in consequence of complete degeneration of the isolated cord segment was found to be fibrillating and of a deeper red than the muscle at rest. It is

concluded, therefore, that atrophy developing under conditions of inactivation without denervation may properly be considered inactivation atrophy, or atrophy of disuse.

ALPERS, Philadelphia.

THE PHENOMENON OF MYOTONIA. D. DENNY-BROWN and S. NEVIN, Brain **64**:1, 1941.

Previous experiments on myotonic goats and patients with myotonia following nerve block have shown that the myotonic after-contraction is associated with rapid oscillatory action potentials. These are of small amplitude, resembling the fibrillation of denervated muscle, and are due to repetitive after-discharge in single muscle fibers. This "peripheral myotonia" is a purely muscular phenomenon, possibly related to disturbance in the sodium potassium ratio in the muscle. However, this phenomenon seen after percussion of the muscle or on nerve stimulation after nerve block is not sufficient to account for the strong, diffuse spasm seen after a willed contraction in the myotonic patient. This "after-spasm" is a sudden, prolonged, fresh contraction released by the patient's effort to relax. It is associated with large action potentials, similar to motor unit discharges. It occurs in the muscles previously involved in the willed movement and in their antagonists. It increases when the voluntary contraction ceases and is stronger and more intense than the strongest voluntary contraction. It is not due to voluntary antagonistic movements, for it occurs after willed movement even if the patient merely attempts to relax.

The "after-spasm" usually seen in the long flexors of the wrist after the grasp does not occur after nerve block of the small intrinsic muscles of the hand. Thus, although due to motor neuron discharge, it is determined primarily by the myotonic condition of these muscles. It is probably a reflex contraction caused by some persistent effect in the proprioceptors of the intrinsic muscles.

Denny-Brown and Nevin conclude that the muscular spasm which is associated with difficulty in relaxing a willed grasping or other movement in myotonic persons is due to a discharge of the central motoneurons. It is thus distinct from the purely muscular phenomenon of delayed relaxation, which, as previously shown, is due to repetitive firing of single muscle fibers. Both conditions serve to contribute to the disability observed in myotonic patients.

MASLAND, Philadelphia.

PERIPHERAL CONDUCTION RATE IN THE SYMPATHETIC NERVOUS SYSTEM OF MAN. E. A. CARMICHAEL, W. M. HONEYMAN, L. C. KOLB and W. K. STEWART, J. Physiol. **99**:338, 1940.

The rate of conduction in postganglionic sympathetic nerve fibers in man was estimated by measuring the elapsed time between the application of a stimulus and the appearance of changes in skin conductivity at a point remote from the stimulus. By measuring changes in conduction time to points requiring longer and shorter conduction paths, a basis for estimating conduction rate was provided. The velocity of conduction was found to vary from 2.17 to 1.80 meters per second in the upper extremity, from 2.30 to 2.03 meters per second in the chest and from 1.27 to 0.85 meters per second in the leg.

THOMAS, Philadelphia.

Neuropathology

SPECIFIC NERVE SHEATH TUMOR OF ORBIT. ANTONIO ROTTINO and AQUIN S. KELLY, Arch. Ophth. **26**:478 (Sept.) 1941.

Rottino and Kelly report a case of orbital neurilemmoma and review the literature concerned with tumors of the orbital nerve. They were able to find only 11 cases in which the growth was sufficiently well described to be classified as a neurilemmoma.

The authors find that neurilemmoma of the orbit is a solitary tumor and that it originates in a nerve sheath and may appear in either the central or the

peripheral nervous system. The neoplasm grows usually at a slow rate, progressively or intermittently, with varying static intervals. The largest tumor reported measured 9 by 4 cm. The tumor is essentially solid and gray and has a specific histologic appearance. It is prone to degenerative changes, which modify its gross and histologic appearance. The symptoms produced are due to its expanding growth, which pushes, crowds and compresses the normal orbital structures. The tumor is benign. It is to be differentiated from solitary neurofibroma and plexiform neurofibroma, which also occur in the orbit. SPAETH, Philadelphia.

AUTOPSY IN A CASE OF DYSTONIA MUSCULORUM DEFORMANS. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **6**:87 (June) 1941.

Nielsen reports the case of a white boy of German descent who was normal until the age of 18 months, when there was an episode of torsion of the spine during a "cold." Thereafter he walked somewhat on his toes, a difficulty which increased, so that at 12 years of age he was considered "spastic" and had begun to have torsion of his arms. An attack of influenza when he was 16 was followed by renewed torsion of the spine and flexion contractures of the legs, which prevented his ever walking again. At the age of 25 he was confined to bed with extreme lordosis and torsion, as well as marked flexion contractures of all the extremities. Passive straightening was possible in the upper extremities and partially so in the lower. He could chew and swallow but not articulate. There were no athetoid movements. The sphincters remained under control. He died at the age of 32, of pneumonia and pneumococcic meningitis. The clinical diagnosis was dystonia musculorum deformans. At autopsy the essential pathologic changes were progressive degeneration of the nerve cells, particularly in the putamen and the dentate nucleus. In the thalamus less marked cellular changes with status marmoratus were observed. Nielsen considers the condition to have been a system disease because of the bilateral involvement of the dentate nucleus and the putamen. MACKAY, Chicago.

A CASE OF INTRADURAL HEMATOMA WITH IPSILATERAL HEMIPLEGIA AND IPSILATERAL THIRD NERVE PALSY. IRVING C. SHERMAN and SIGMUND KRUMHOLZ, J. Nerv. & Ment. Dis. **95**:176 (Feb.) 1942.

Sherman and Krumholz report the case of a man who presented signs of increased intracranial pressure, partial palsy of the left third nerve and left hemiparesis. The clinical impression was that of a space-occupying lesion, either a neoplasm or a subdural hematoma of the right cerebral hemisphere. Autopsy revealed a massive intradural hematoma overlying the anterior two thirds of the left cerebral hemisphere and herniation of the hippocampal gyri, that on the left being much larger. Lateral to each herniation was a deep sulcus, representing the firm edge of the tentorium. The left third nerve was stretched and flattened over the anterior tip of the herniation, and the partial oculomotor palsy on the left side is explained on this basis. The authors believe that the large left-sided herniation tended to push the midbrain to the right, forcing the right cerebral peduncle against the edge of the tentorium and producing left hemiparesis by damage to the right pyramidal tract. CHODOFF, Washington, D. C.

NEUROPATHOLOGICAL FINDINGS IN THE BRAIN AND SPINAL CORD OF CHRONIC ALCOHOLIC PATIENTS. LEO ALEXANDER, Quart. J. Stud. on Alcohol **11**:260 (Sept.) 1941.

Alexander describes the pathologic changes in the brain and spinal cord of alcoholic patients and divides them into those which are recognizable grossly and those which can be recognized only by microscopic examination. He finds that grossly the brains of patients who die of acute alcoholism show hyperemia and swelling, with a corresponding reduction of fluid in the subarachnoid space. He states that the frequent occurrence of subdural hemorrhage in alcoholic persons is

probably due to major or minor trauma as a contributing cause or an eliciting factor. He divides the microscopic changes into (1) those in which the neural parenchyma is damaged directly and primarily, best summarized under the term neuronitis, and (2) those in which the neural parenchyma is affected only indirectly by means of damage to the vascular system, a syndrome which has been termed Wernicke's disease. The author states that this disease has been reproduced in his laboratory in a series of animal experiments adapted to create a state of vitamin B_1 deficiency more severe than that which is sufficient to cause neuronitis. This experimental disease was found to be topographically and histopathologically identical with Wernicke's disease in man. He concludes that it is justifiable to regard Wernicke's disease as due to a depletion of vitamin B_1.

The cerebellar degeneration observed in chronic alcoholism appears pathologically to stand somewhat between that in neuronitis and that in Wernicke's disease. Alexander has also observed an identical type of degeneration in patients with juvenile diabetes. He concludes that the majority of pathologic conditions encountered in the nervous system in chronic alcoholism are attributable to associated vitamin deficiencies, particularly vitamin B_1, nicotinic acid and vitamin C. These vitamin deficiencies are due to increased intake as a result of the alcoholic patient's choice or habit, decreased utilization by the diseased gastrointestinal tract, increased requirements resulting from the added caloric burden of metabolism and, possibly, to a still unascertained specific destructive chemical effect of alcohol and fusel oil (amyl alcohol) on ingested vitamins.

BRACELAND, Chicago.

Psychiatry and Psychopathology

A POST-REPEAL STUDY OF 300 CHRONIC ALCOHOLICS. JAMES V. LOWRY and FRANKLIN G. EBAUGH, Am. J. M. Sc. **203**:120 (Jan.) 1942.

Lowry and Ebaugh studied 300 patients with alcoholism admitted during the years 1936 to 1939, since this period represented an increase in the number of patients following the repeal of the Eighteenth Amendment. Fifty-seven (19 per cent) of the patients left in less than a week, indicating a superficial desire to get well. The preference of the patients was mostly for whisky, and 107 (36.3 per cent) were periodic drinkers. Ninety-eight (32.7 per cent) of the patients were classified as psychotic on admission; 22 (22.4 per cent) of the 98 psychotic patients and 24 (11.9 per cent) of the 202 patients without psychosis had peripheral neuritis. Chronic alcoholism was said to exist in 170 (56.7 per cent) of the series by the age of 30. A history of infidelity, impotence or perversion was obtained in about 15 (50 per cent) of the 30. One hundred and six (41.4 per cent) of the 256 patients who had been married were either divorced or separated. Poor emotional adjustment was apparent in childhood in 95 (31.7 per cent). Sixty-two were "nervous," stubborn, pouty, shy, enuretic or had night terrors. Although there was improvement in 246 (82 per cent), only 18 (6 per cent) were given a good prognosis on discharge. As far as could be determined, 20 per cent of the 300 patients had not been intoxicated for a minimum of six months after leaving the hospital.

MICHAELS, Boston.

THE HEREDITARY FACTOR IN MENTAL DEFICIENCY. A. T. HOPWOOD, C. C. KIRK and F. L. KEISER, Am. J. Psychiat. **98**:22 (July) 1941.

Hopwood, Kirk and Keiser studied thousands of records from institutions for the feebleminded and the state hospitals, as well as thousands of commitment papers. They excluded all instances of feeblemindedness in which there were organic factors, such as cretinism or mongolism. In this manner, they obtained material on 1,765 families. In 821 families with evidence limited to one generation the authors found 1,880 siblings or cousins who were mentally defective, epileptic or insane. In 317 of the 827 families in which the evidence was confined to two generations, mental deficiency was found in the parents. There were 1,161 mentally

defective children, and for the 827 families 2,334 persons were mentally defective, epileptic or insane. Furthermore, in 115 families in this group one or both parents and one or more children were mentally defective. Among 114 families which were studied for three generations there were 256 mentally defective persons. Hopwood, Kirk and Keiser point out the preponderance of morons and imbeciles over idiots (85 : 15 per cent). They conclude that it is safe to assume that in 50 per cent of their cases the conditions could be attributed to heredity.

FORSTER, Boston.

FACTORS IN SUICIDAL ATTEMPTS. DWIGHT M. PALMER, J. Nerv. & Ment. Dis. **93**:421 (April) 1941.

Twenty thousand successful attempts at suicide are reported annually in the United States, but this figure represents only a part of the problem because of the large number of genuinely motivated but unsuccessful attempts, as well as the attempts which are unrecognized or covered up. Among the motives for suicide are (1) the wish to kill in order to destroy undesirable elements in the self, such as strivings for murder, incest and homosexuality, to cause another person regret, to kill another person now dead with whom the person has identified himself or to kill the self as a substitute for an object that has been removed, leaving unneutralized hate; (2) the wish to be killed in order to obtain punishment or to satisfy masochistic strivings, and (3) the wish to die in order to obtain reunion with a deceased person or with God, to obtain atonement or to find a more congenial environment.

In a study of 25 cases of unsuccessful suicide, Palmer made a longitudinal examination of the life history of each patient in an effort to discover the psychologic bases for the act. Seventeen of the patients were males and 8 females. In the life stories, Palmer discovered failure to make a successful heterosexual adjustment, as evidenced by failure to marry or by separation or divorce in 12, or 48 per cent, of the cases. Chronic alcoholism was present in 7, or 28 per cent, of the cases and was considered evidence of a fixation of psychosexual development. Minor forms of self-mutilation were found, such as nail biting in 2 cases and tattooing in 1. An important feature was the early death or absence of a parent or sibling in 21, or 84 per cent, of the cases. In 40 per cent the parent of the opposite sex, and in 20 per cent the parent of the same sex, was lost before the patient reached the age of 14 years. Such a loss may influence a young person by representing a loss of a libido-invested object, a loss of an object normally used as a transition unit in psychosexual development or a loss of superego material. Palmer concludes that the alleged "cause" of the suicide is, at most, only a precipitating event, that the basis for the attempt is laid in the early, formative years of the personality, that the suicidal person is fundamentally selfish and that the basic mechanism in a majority of suicidal attempts is an arrest in the psychosexual development of the person.

MACKAY, Chicago.

A COMPARATIVE STUDY OF RECOVERED AND DETERIORATED SCHIZOPHRENIC PATIENTS. OTTO KANT, J. Nerv. & Ment. Dis. **93**:616 (May) 1941.

Kant studied the clinical features in a group of 39 completely recovered and a group of 39 deteriorated schizophrenic patients in an effort to discover criteria of prognostic value. The psychoses in the cases of patients who had recovered were predominantly characterized by an acute onset, apparently psychogenic precipitation, the presence of clouding of consciousness at the beginning of the illness, a tendency to extroversion and a pyknic physique. These features were six times as common in cases ending in recovery as in those ending in deterioration. In addition, patients who had recovered from more than one psychotic episode had apparently recovered completely between attacks, while all but 2 deteriorated patients had continued to exhibit abnormalities after the first attack. Among those patients who recovered, only those psychoses resembling atypical depressive

states had a gradual onset but in these the absence of clouding of consciousness and the less intense schizophrenic symptomatology served as distinguishing features. When an acute onset was present in a psychosis leading to deterioration, bizarreness, an autistic trend and lack of coherence indicated the unfavorable prognosis.

MACKAY, Chicago.

THE ROLE OF DETECTIVE STORIES IN A CHILD ANALYSIS. EDITH BUXBAUM, Psychoanalyt. Quart. **10**:373, 1941.

Buxbaum reports the analysis of a 12 year old boy who was referred for treatment because of severe anxiety and inability to learn at school. The latter symptom was caused by the fact that he spent his entire time reading detective thrillers, which he felt under a compulsion to read. Analysis revealed that by this compulsion he could avoid feelings of anxiety. When he read the stories he made the detective his ego ideal whom he wanted to be like because his role was one which protected the victim of the crime and hindered the criminal. Unconsciously he identified himself with the victim of the story, who represented his passive wishes to be overcome and castrated. These wishes were frightening and were in conflict with his unconscious identification with the criminal, i. e., with his aggressive feelings against his sister, his mother and his uncle (his father was dead), which he feared lest they result in his castration.

PEARSON, Philadelphia.

ON THE POSSIBLE OCCURRENCE OF A DREAM IN AN EIGHT MONTH OLD INFANT. MILTON H. ERICKSON, Psychoanalyt. Quart. **10**:382, 1941.

Erickson reports the following observations on an infant which seemed to indicate that the child was dreaming. Her father was accustomed to play with her for a brief period each evening, just before she had her evening feeding. When she was exactly 8 months old he was absent from home on two successive nights. He returned in the evening after she was asleep and went into her room. Suddenly she started to go through the motions she made in her play, laughing as she did so. He left the room, and she did not awake. When she was 13 months old she started to laugh loudly in her sleep, which was so sound that even the changing of her diaper did not awaken her. When she was 23 months old her older sister fell and hurt her knee and the baby was much concerned. That night she started to cry in her sleep, saying "Carol [the older sister] bad bump." She was difficult to arouse, and when she awoke she seemed to be astonished that her sister was sleeping in the next bed.

PEARSON, Philadelphia.

WHAT PHYSICIANS EXPECT FROM PSYCHIATRY. ELLIOT C. CUTLER, War Med. **1**:352 (May) 1941.

Cutler emphasizes that the Army should pay marked attention to the opinion of psychiatrists as to whether a draftee is accepted or rejected. He points out the loss entailed by the selection of undesirable recruits and believes these dangers can be avoided by the further use of psychiatrists by the local draft boards.

PEARSON, Philadelphia.

AETIOLOGY OF THE FUGUE STATES. E. STENGEL, J. Ment. Sc. **87**:572 (Oct.) 1941.

The intimate similarity of fugue states associated with different types of mental disorder led Stengel to investigate the possibility of there being etiologic factors common to all of them. His findings reveal hitherto unrecorded facts regarding this interesting type of compulsive wandering. The clinical relation between fugue states and epileptic conditions is well known but imperfectly understood, but heretofore no attention has been given to the relation of fugue states to the manic-depressive constitution. The author believes that the case material of his

paper shows some tendency toward endogenous periodic changes of mood which could be demonstrated in nearly all cases of fugue, and in some this feature was hereditary. The constitutional relation to the manic-depressive reaction types was not dependent on other features of the manic-depressive reaction and could be traced in epileptic persons as well as in patients with hysterical and other psychopathic symptoms. Stengel believes that this represents a feature which can be regarded as common to patients subject to fugue states, irrespective of the nature of any other coexisting mental disorder. In Stengel's cases the fugue states were obviously associated with spells of depression or, less commonly, of elation of the endogenous type.

One striking fact was found to be common to all the cases of compulsive wandering, namely, a serious disturbance in the child-parent relationship and a consequent abnormal family life. A considerable number of the patients displayed a tendency to habitual lying; fantastic tales were woven about their family origin —obviously, a desire to replace the realities of their unhappy childhood by wish fantasies. The fact that special environmental conditions are indispensable for the origination of compulsive wandering leads the author to state that their nature cannot be understood without psychogenetic interpretation. He insists, however, that such interpretation cannot completely explain the condition which is certainly caused by the interaction of psychogenetic and constitutional and other factors. This very combination of factors plus the necessary environmental abnormalities explains the comparative rarity of the fugue state, which he believes bears characteristics of a symbolic act. There appear, therefore, to be three essential conditions without which fugue states do not develop: a tendency to indulge in periodic changes in mood, a disturbance of home conditions in childhood and a tendency toward the production of twilight states, the last factor being most prominent in epileptic persons. In the author's cases compulsive wandering was often associated with a short period of loss of sexual control.

Stengel also draws attention to the bearing which his findings have on two problems of special interest under present war conditions: The first is that of the possible consequences of the break-up of the family life on children, and the second, that of the psychologic background in certain cases of desertion from military service.

BRACELAND, Chicago.

Diseases of the Brain

CEREBRAL AIR EMBOLISM FOLLOWING ANTRAL IRRIGATION. FRANCIS HENRY McGOVERN, Arch. Otolaryng. **34**:593 (Sept.) 1941.

Cerebral and cardiac air embolism may follow the introduction of air into cavities of the body. The antrum, eustachian tube, thorax, knee joint, varicose veins and great vessels of the neck have been the site from which the embolism originated. It is dangerous to use air to blow the saline solution from the antrum. Air should not be used to determine the patency of the ostium. The symptoms of air embolism are abrupt in onset. The patient may have local pain, with anxiety, restlessness, sudden pallor, local followed by general convulsions, irregular pulse, unconsciousness and stertorous respiration, and death may follow. Milder degrees of air embolism may result in coma, temporary hemiplegia and blindness. The condition is frequently misdiagnosed as cocaine poisoning. Mild cocaine poisoning is marked by excitement, talkativeness, acceleration of the pulse, dilatation of the pupils, a feeling of well-being and slight convulsive movements. Fainting and collapse, with slowing and weakening of the pulse, shallow respiration and general depression followed by death, come from absorption of large amounts of cocaine. A patient surviving air embolism fifteen minutes has a good chance of recovery. The author reports 2 cases. In 1 case a Lichtwitz needle was inserted beneath the inferior turbinate into the right maxillary sinus. After the insufflation of air and withdrawal of the needle the patient died. In the second case a curved cannula was passed through the natural ostium and pus washed from the antrum.

Air was insufflated. Immediately on withdrawal the patient had a severe generalized convulsion with stertorous breathing. On recovery from the convulsion she remained in a partial coma and exhibited extreme restlessness. The anesthetic used was 2 per cent cocaine. The blood sugar measured 312 mg. per hundred cubic centimeters, but the absence of acetone bodies in the urine and the absence of the usual picture of diabetic coma made the consulting physician, Dr. S. C. Hall, feel that the case was one not of diabetic coma but of cerebral air embolism following artificial pneumothorax. Within a week recovery was complete.

HUNTER, Philadelphia.

AUTOPSY OF BRAIN IN CASE OF SIMULTANAGNOSIA. ARNOLD P. FRIEDMAN and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **6**:79 (June) 1941.

Friedman and Nielsen report the case of a man aged 68, who after a cerebral vascular accident exhibited right homonymous hemianopia, hemiparesis and hemihypesthesia. He read without comprehension (semantic alexia) and when shown pictures was unable to recognize the action represented (simultanagnosia). At necropsy marked cerebral arteriosclerosis was discovered, with occlusion of the left posterior cerebral artery, destruction of the left cerebral peduncle and softening of the left cuneus and lingual gyrus, as well as the left thalamus posteriorly. The inferior portions of areas 18 and 19 of Brodmann on the left side were destroyed, but the convex portions of both areas were preserved. The cortex of area 19 was destroyed on the right side. The left superior cerebellar artery was also thrombosed. The authors point out that the term simultanagnosia represents not loss of recognition of simultaneity but failure to elaborate visual impressions into terms of sequence. He attributes the symptom in this case to interruption of the connections between the left area 19 and the thalamus. The right occipital lobe could not elaborate visual impressions since its area 19 was destroyed.

MACKAY, Chicago.

AGENESIS OF THE CORPUS CALLOSUM. LEON N. GOLDENSOHN, E. RUCKER CLARDY and KATE LEVINE, J. Nerv. & Ment. Dis. **93**:567 (May) 1941.

Goldsohn, Clardy and Levine report the case of a Jewess aged 11 years 10 months. She had a maternal cousin, a woman aged 40, who had been mentally unbalanced since 9 years of age. The patient was the older of 2 children and was born normally at full term. Development had been normal except for occasional diurnal enuresis and soiling. When 9 years old she began to gain weight rapidly. With the onset of menstruation, at the age of 10 years 9 months, she began to have frontal headaches and dizziness. Since the age of 2 years she had had temper tantrums. When 7 years old her intelligence quotient was 102, but her school work lagged because of misbehavior and precocious sexual behavior. When 11 years old her intelligence quotient was 88. Neurologic examination showed slight right external strabismus, weakness of the right side of the face of supranuclear type, defective arm swing and dysdiadokokinesis on the left, slight static tremor of the hands and an increased patellar reflex and a positive Babinski reaction on the right. The patient was hypomanic in a flighty, silly, monotonous, repetitive, ingratiating manner, with stereotypy, impulsive speech, rapid emotional changes and vacuous expression. She was mildly paranoid toward other children but was afraid of boys. During her temper tantrums she ran about screaming until she became cyanotic. Numerous psychologic tests revealed mild mental retardation, with slow association and defective ability for generalization and abstraction. The Rorschach test gave evidence of organic disease of the brain. Electroencephalographic examination revealed marked irregularity throughout the record, with slow waves and asymmetry between the two hemispheres, suggesting diffuse cortical dysfunction. Pneumoencephalographic examination disclosed dilatation and upward displacement of the third ventricle, enlargement and divergence

of the occipital horns, radial appearance of the sulci on the medial aspect of the brain and their extension through the zone usually occupied by the corpus callosum. The diagnosis was agenesis of the posterior portion of the corpus callosum with internal hydrocephalus. The patient exhibited a constant slight elevation of temperature. Two months after admission she began to have major convulsive seizures. Goldensohn, Clardy and Levine believe that emotional factors colored the clinical picture in this case and refuse to outline any clinical syndrome of the corpus callosum.

MACKAY, Chicago.

SLEEP PARALYSIS. BEN W. LICHTENSTEIN and ALFRED H. ROSENBLUM, J. Nerv. & Ment. Dis. **95**:153 (Feb.) 1942.

Sleep paralysis is defined as transient paralysis occurring when the patient is going to sleep or awakening from sleep. The condition was described in 1876 by S. Weir Mitchell. Lichtenstein and Rosenblum report the case of a woman aged 69 in whom transient episodes of complete paralysis on awakening from sleep had occurred since childhood. The results of neurologic examination were without significance, and except for mild diabetes the patient was in good health. The authors point out that this is an example of what Pavlov called localized sleep, the motor centers being "asleep" while "consciousness" is awake. The frequent association of narcolepsy with sleep paralysis is noted. The condition should be differentiated from familial periodic paralysis.

CHODOFF, Washington, D. C.

THE ALLERGIC FACTOR IN IDIOPATHIC EPILEPSY. D. C. DEWAR, J. Ment. Sc. **87**:608 (Oct.) 1941.

Dewar reviews the subject of the possible association of epilepsy with food sensitization, starting with the work of Spratling, in 1904. His study of the literature suggested the existence of considerable opportunity for further research. He examined three groups of patients, each group consisting of 24 persons. The first consisted of adults with idiopathic epilepsy. The second and third groups were picked at random from psychotic patients without epilepsy and the staff, respectively. The only common factor stressed was an approximation of the average age of the three groups.

The presence of allergic phenomena in the epileptic group was almost twice that of the other two classes combined. Actually, 66 per cent of the patients with epilepsy gave a personal or familial history of allergy. Each group was given cutaneous tests with group reagents and individual allergens. One week later the subjects were tested intradermally with a solution of proportionately modified strength. The final recording of positive results was based on intradermal responses irrespective of a corresponding negative or positive scratch reaction. Fourteen epileptic patients gave positive reactions.

An interesting side light on the study indicates that the psychotic patients displayed a greater degree of allergic response than did the normal controls. The 14 epileptic patients were finally tested with individual allergens in an attempt to isolate the offending protein. The patients were then treated by means of intramuscular desensitization; after the fifth injection 2 patients, both sensitive to cheese, had fits; one of them died in what might have been coincidental status epilepticus.

The results of the desensitization of the remaining 12 epileptic patients is summarized as follows: (*a*) distinct improvement in incidence of fits and in the mental condition, 3 cases; (*b*) a lesser degree of improvement in incidence of fits and in the mental condition, 1 case; (*c*) improvement in incidence of fits alone, 3 cases; (*d*) improvement in the mental condition alone, 1 case; (*e*) no improvement, 3 cases; (*f*) death while under observation, 1 case.

The author concludes that his work confirms the postulated relation between allergy and epilepsy, the supporting facts being (1) the preponderance of allergic manifestations in the personal and family histories of the epileptic patients; (2) the greater sensitivity of the epileptic group to cutaneous tests; (3) the loss or

diminution following desensitization of cutaneous sensitivities in all but 1 patient; (4) the association of sensitivity to a specific protein and seizures in the histories of 4 patients, and (5) the alleviation of symptoms by specifically directed treatment through elimination and desensitization in 9 patients.

BRACELAND, Chicago.

CUTANEOUS NAEVUS WITH BUPHTHALMOS AND EPILEPSY. REDVERS IRONSIDE and DENNIS HILL, J. Ment. Sc. **87**:631 (Oct.) 1941.

Ironside and Hill describe a case of Sturge's syndrome, so-called because in 1879 Sturge gave the first complete account of a rare syndrome comprising the coexistence of naevus flammeus of the skin, glaucoma or buphthalmos and epilepsy.

The naevus flammeus appears characteristically over one side of the face within the distribution of the divisions of the trigeminal nerve. In the authors' case it extended over various segmental areas of the body. The buphthalmos or glaucoma occurs on the same side as the facial nevus. Within the cranial cavity two types of lesions have been described: (*a*) a venous cavernous angioma of the meninges and brain, sometimes penetrating as deep as the ventricular system, or (*b*) telangiectasis of the pia-arachnoid, with shrinkage and sclerosis of the underlying cortex and deposits of lime salts in the second and third cortical layers but not in the pial vessels. Weber added a fourth sign to the syndrome, the characteristic appearance of the roentgenograms of the skull.

The case described by the authors is that of a soldier with naevus flammeus and buphthalmos, who had repeated fits on the opposite side of the body while on duty with his unit. He was of low mentality but by no means mentally defective. Roentgenograms of his brain showed no calcification of the cerebral sulci. The contralateral fits which the patient described resembled migrainous attacks since they were preceded by teichopsia. The loss of consciousness and residual transient paresis of the left arm and leg, however, render it probable that he suffered from a type of jacksonian epilepsy, though no fit was actually witnessed in the hospital. In this patient no heredofamilial incidence of the syndrome in whole or part could be ascertained. The article contains a good list of references on this unusual syndrome.

BRACELAND, Chicago.

THE APALLIC SYNDROME. ERNST KRETSCHMER, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:576 (May) 1940.

In addition to the better known mental changes resulting from acute intoxication and chronic disease of the brain, such as coma, delirium and dementia or intellectual enfeeblement, Kretschmer describes what he chooses to call the "apallic syndrome." These patients show marked and persistent blocking of motor and intellectual processes. They lie quietly in bed with little spontaneous movement, usually staring vacantly ahead without fixating. They fail to respond to simple commands, do not respond to objects or people placed before them and often show cataleptoid tendencies, remaining in uncomfortable positions for long periods. Paradoxically, they overreact at times to even minor stimuli, occasionally with twitchings. Swallowing and other vegetative functions remain intact. The sucking and grasp reflexes are often active. Extrapyramidal phenomena, such as dyskinesias, may or may not be present. The blocking of all functions is characteristic.

The designation "apallic syndrome" refers to the more or less sudden interference with activity of the whole cortex. Focal phenomena, due to involvement of discrete portions of the cortex, do not necessarily have to be present. The clinical picture is encountered most frequently in diffuse encephalitic processes, with predominant involvement of the cortex. It is also found in cases of trauma to the head, especially gunshot wounds, widespread cerebral syphilis and disseminated foci of softening due to arteriosclerosis.

SAVITSKY, New York.

Treatment, Neurosurgery

A Comparison of the Results of Metrazol Therapy with a Group of Matched Controlled Cases. J. B. Craig and M. E. Schilling, Am. J. Psychiat. **98**:180 (Sept.) 1941.

Craig and Schilling studied two groups of patients with schizophrenia, of 23 each. Each group represented the same distribution with respect to diagnosis, age, duration of hospitalization, duration of illness before admission, hereditary factors, premorbid personality, premorbid achievement, neuropathic traits, mental status and chief symptoms. One of the groups received metrazol therapy. Craig and Schilling found that only 3 of the group treated with metrazol remained unimproved whereas 13 of the other group remained unimproved.

Forster, Boston.

Effect of Benzedrine on the Oculogyric Crises of Parkinsonism. H. Lovell Hoffman, Brit. M. J. **1**:816 (May 31) 1941.

Hoffman reports the effect on the oculogyric attacks in 17 cases of post-encephalitic parkinsonism following the administration of amphetamine (benzedrine) in conjunction with drugs of the belladonna group. Good results were obtained in 23.5 per cent, moderately good in 29.4 per cent and poor in 47 per cent of cases. The author cites three American authors who obtained improvement in 100 per cent of cases after the administration of larger doses of the drug. He concludes from his investigations that relief of oculogyric crises can be expected in 50 per cent of cases even from small doses of amphetamine if given with drugs of the belladonna group.

Echols, New Orleans.

Employment of Air-Raid Noises in Psychotherapy. F. L. McLaughlin and W. M. Millar, Brit. M. J. **2**:158 (Aug. 2) 1941.

McLaughlin and Millar observed that treatment of neuropathic military patients along standard psychotherapeutic lines was impeded by too quiet an environment in the hospital. Psychotherapy was effective against all symptoms except a certain hypersensitivity to air raid noises. The authors, therefore, attempted to "decondition" this hypersensitivity by reproducing warfare noises until the patient's reaction to them gradually became more normal. Records of actual bombing noises and reassurance talks were used. The procedure was also used as a speedy and practical method of abreacting patients.

Echols, New Orleans.

Alcoholization of Intercostal Nerves in Therapy of Fractures of Ribs. G. Radici, Gazz. d. osp. **61**:603 (July 28) 1940.

Radici reports 40 cases of fracture of ribs, with or without pleuropulmonary complications, treated by the Latteri technic. The method consists in roentgenologic identification of the fractured rib or ribs and injection of 0.5 cc. of a 4 per cent solution of procaine hydrochloride followed thirty seconds later by the injection of 2 cc. of 90 per cent alcohol 4 cm. away from the vertebral spinous process, perpendicular to the posterior costal plane of the vertebral spinous process and along the lower margin of the rib up to the costal sulcus. The alcohol is injected slowly. This procedure is repeated for each fractured rib in one treatment, except in the presence of several fractured ribs in old persons. In the elderly, alcoholization is carried out in two or three treatments. In the cases reported local pain caused by respiration was immediately and permanently controlled, and the course of the pleuropulmonary complications, such as emphysema, hemothorax and hemoptysis, was favorably influenced. The author believes that the treatment stimulates normal formation of callus. It is simple and well tolerated. The nerves regenerate within two or three months.

J. A. M. A.

Muscular System

OCULAR MANIFESTATIONS IN MYASTHENIA GRAVIS. ROBERT DEAN MATTIS, Arch. Ophth. **26**:969 (Dec.) 1941.

Mattis made a survey of ocular symptoms associated with myasthenia gravis based on 26 cases. In 25 of these ocular symptoms were shown at some time during the course of the disease. In 90 per cent of cases diplopia and in 85 per cent ptosis were present on one or more occasions; in 46 per cent ptosis was the first subjective symptom; in 4 per cent ptosis was present as a bilateral simultaneous situation; in 19 per cent ptosis involved only one lid throughout the course of the disease; in 73 per cent ptosis was intermittent, involving the two lids singly in irregular alternation throughout the course of the disease; in 77 per cent ptosis and diplopia appeared simultaneously on some occasions; in 34 per cent diplopia was the first subjective symptom, and, finally, in 65 per cent some ocular symptom was the first subjective indication of the disease. The ocular manifestations as listed were considerably more common in this series than in those reported by previous investigators. As a result of this study Mattis expresses the belief that the ocular manifestations of myasthenia gravis are much more common than is generally thought, that they are due not to a contracted state of the musculature involved but to some neuromotor dysfunction that is considerably benefited by the administration of prostigmine and that the ophthalmologist is afforded excellent diagnostic aid in the form of intramuscular injections of prostigmine methylsulfate.

SPAETH, Philadelphia.

COMBINATION OF HEREDOATAXIA AND PRIMARY MYOPATHIA. L. BENEDEK and R. BAK, Confinia neurol. **3**:348, 1941.

Benedek and Bak describe instances of Friedreich's ataxia occurring in 2 siblings. One of the patients, in addition to the usual manifestations of Friedreich's disease, had primary myopathy of the Leyden-Möbius type, involving the musculature of the pelvis and trunk, associated with endocrine disturbances of hyperpigmentation, hypertrichosis and virilism.

DEJONG, Ann Arbor, Mich.

Diagnostic Methods

ROENTGENOSCOPY OF PHARYNX IN MYASTHENIA GRAVIS BEFORE AND AFTER PROSTIGMINE INJECTION. R. S. SCHWAB and H. R. VIETS, Am. J. Roentgenol. **45**:357 (March) 1941.

Since dysphagia occurs in about 60 per cent of patients with myasthenia gravis and since it is the third most common symptom in the disease, it seemed important to Schwab and Viets to recognize dysphagia when it first occurs and to estimate how severely the pharyngeal muscles are involved. The authors took advantage of the fact that in myasthenia gravis the pharyngeal muscles are affected by prostigmine to demonstrate the response to the drug in 19 patients by roentgen visualization of the pharyngeal cavity during ingestion of barium sulfate. A group of patients with other forms of dysphagia were similarly studied. Of the 19 patients so examined, 17 responded so strikingly to an injection of prostigmine methylsulfate that practically no barium sulfate was retained in the pharynx. The same patients had also done well under treatment with prostigmine bromide by mouth. The technic of roentgenoscopic examination is described. In a case of severe form, before the intramuscular injection of prostigmine methylsulfate, the thin barium will be retained in the pharynx in such a manner as to be obvious on the roentgenogram. Fifteen minutes after injection, it is only in patients with myasthenia gravis that the barium passes through the pharynx in a normal manner. The degree of improvement in swallowing, as demonstrated by this method, is an excellent adjunct to the "prostigmine test."

J. A. M. A.

A Modified Babinski Reflex (Resistance Reflex). E. Lichtmann, J. Nerv. & Ment. Dis. **93**:451 (April) 1941.

Lichtmann describes a sign which he has discovered in patients suffering from lesions of the pyramidal tract. While lying on his back the patient is requested to raise one of his legs against the examiner's firm downward pressure, applied either above or below the knee. The reflex is considered to be elicited when the great toe becomes extended ipsilaterally or contralaterally or when all the toes exhibit a fanlike spread associated with their dorsiflexion. This "resistance reflex" was found in 47 cases of central lesions, including apoplexy, intracranial neoplasms, subacute combined degeneration of the cord, multiple sclerosis and cerebral concussion and contusion. The sign occurred almost always before the appearance of other signs of involvement of the pyramidal tract, and it often persisted after their disappearance. Lichtmann believes that the reflex has a pathway of its own, since it seems to be more than a modification of the Babinski reaction and, unlike the latter, requires the cooperation of the patient.

Mackay, Chicago.

Cisterna Magna Lead for Electroencephalography. Roy R. Grinker, Confinia neurol. **3**:257, 1941.

Grinker describes the use of a specially constructed obturator which may be inserted into the cisterna magna and used as a lead in electroencephalographic studies. Characteristic waves are elicited, which he believes originate in the medulla. The tracings reveal transmitted, and possibly untransmitted, alpha waves and characteristic 50 per second gamma waves, which, when enlarged, show undulations synchronous with pulsations of the cerebrospinal fluid. He suggests that a study be made of the gamma rhythm in normal and in pathologic conditions by means of the cisternal lead.

DeJong, Ann Arbor, Mich.

Basal Ganglia

Hepatolenticular Degeneration (Wilson's Disease) Following Splenectomy: Interrelationship of Reticuloendothelial and Central Nervous System. A. M. Rabiner, H. Joachim and I. S. Freiman, Ann. Int. Med. **14**:1781 (April) 1941.

Rabiner and his associates report 2 instances of a heretofore unrecorded sequel to splenectomy. Symptoms indicating hepatolenticular degeneration followed soon after splenectomy performed for anemia and purpura associated with splenomegaly. The symptoms direct attention to a possible contraindication to splenectomy. In the first case mild parkinsonian tremors of four years' duration followed a febrile illness diagnosed as typhoid. The tremors were most likely due to striatal disease dating back to the febrile illness of four years before. This tremor was not associated with any gross disability. After the splenectomy the tremor and the muscular rigidity were soon extreme and the Kayser-Fleischer ring was noticed for the first time. The neurologic disorder then progressed rapidly. The splenectomy probably aggravated the striatal disease. The other patient had chronic hemorrhagic diathesis for many years. Headaches, blurred vision and slowing up of activities suggested that the symptoms were due to epidemic encephalitis. However, none of the objective symptoms of disease of the basal ganglia was present until two months after the splenectomy, when the entire neurologic syndrome was initiated and progressed rapidly and resembled hepatolenticular disease. For a time the course remained stationary. Almost two years after the operation, in a fit of despondency, the first patient committed suicide. Necropsy revealed typical features of Wilson's disease. While the changes were diffuse, they were far more marked and advanced in the basal ganglia, thalamus and hypothalamus. A large number of type II glia cells of Alzheimer, typical of Wilson's disease and pseudosclerosis, were found in these areas. The authors feel that the condition in this

case must be placed in the category of hepatolenticular degeneration. While it does not fulfil the original pathologic criterion of Wilson, cystic degeneration of the putamen, nevertheless degeneration in this region, with formation of a spongy state, was prominent and the friability lead the authors to believe that cystic degeneration might ultimately have ensued. The changes, while diffuse, did not follow the typical description of pseudosclerosis, which includes diffuse and widely scattered Alzheimer cells. The authors expressed the belief that they were dealing with a form of hepatolenticular degeneration intermediate between Wilson's disease and pseudosclerosis. It is apparent that removal of the spleen was not the primary etiologic factor responsible for the onset of hepatolenticular disease, as in each case the disease had existed preoperatively. This was shown by cirrhosis of the liver observed at operation and by the preoperative existence of minimal neurologic symptoms the significance of which had been overlooked. It was present in a latent or subclinical form, and operation accelerated the process. J. A. M. A.

Diseases of Skull and Vertebrae

TUBERCULOUS SPONDYLITIS. BERNARD N. E. COHN, Arch. Path. **32**:641 (Oct.) 1941.

Cohn reports the pertinent histopathologic observations in 13 cases of tuberculous spondylitis. He concludes as follows: 1. The intervertebral disk is attacked early in the course of the disease. The fibrocartilage and nucleus pulposus are destroyed before the hyaline portion of the disk. 2. The intervertebral disk may be invaded either directly from the contiguous subchondral marrow spaces or from the longitudinal ligaments after these have been invaded by the tuberculous process. 3. Areas of regenerating osseous and hyaline cartilaginous tissues are found in the reparative stages. 4. Obliterative endarteritis is frequently observed in active foci. The tuberculous process may extend from one body to another along the longitudinal ligaments. WINKELMAN, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

ABRAHAM A. BRILL, M.D., *President, New York Neurological Society, Presiding*
Joint Meeting, Jan. 6, 1942

Anxiety Neurosis of Seventy Years' Standing. DR. C. P. OBERNDORF and DR. ARNOLD EISENDORFER (by invitation).

The clinical history of a woman aged 79 is presented as exceptional in that the patient's compulsions and phobias associated with extreme anxiety have existed almost uninterruptedly for over seventy years without affecting her general physical condition or her intellectual functions.

The patient dated her onset of her symptoms at the age of 5 years, when, with the beginning of masturbation, she became self conscious, had feelings of guilt, was afraid of strange people and was increasingly dependent on and fearful of her mother. The fear of fire and the compulsion to listen for fire engines, which later extended to many other unrelated noises, began at this time.

On at least four occasions aggravation of the symptoms required hospitalization. Each of the hospital records was similar in the description of her illness, and in each the diagnosis of psychoneurosis was made.

At the age of 50 she was referred to Dr. Oberndorf, who by therapy consisting largely of persuasion and reassurance enabled the patient to carry on her life without complete subjugation of her fears.

This patient's neurosis raises the question why and how neurotic formations continue so separated from the main stream of thought flow without contaminating it. Perepel, however, expressed the opinion that "degradation of the personality" results and "that the state of perpetual excitement of the neurotic . . . cannot but result in the wearing out of the brain." This was not true in this case, in which compulsions that the patient recognized as being alien and at cross purposes with the rest of her character caused no deterioration.

The question is considered whether anxiety in itself, when once mobilized, may not constitute an agency of security which is more acceptable than the greater danger against which it had been called into being. Patients have been known to feel the absence of such anxiety as an abnormal and disagreeable sensation.

DISCUSSION

DR. C. P. OBERNDORF: The patient could not be here this evening because she resides some distance away. When I examined her about ten days ago, she showed remarkable alertness. She is now a woman of 79, who is fully in contact with life and knows what is going on in the world. She has a good memory, a sharp tongue and a fine sense of humor. During the first ten years of the long period in which I have been in contact with this woman, now over twenty-eight years, I saw her on an average of two to three times a year. Then she would disappear from observation, and I would see her after a year or two, or she would telephone me. During all this time she has never been free from intense anxiety and pronounced phobias of one kind or another, and has suffered particularly from the fear of noises. This fear has made life difficult for her because she cannot find any place to live where she will be free from noises.

It has occurred to me, as the years have passed, that her excellent health and mentality are unusual. One is inclined to believe that worry wears down people

so that they disintegrate rather early; yet here is a woman who has had such constant anxiety that she has been unable to sleep soundly for nearly sixty years, and on a number of occasions the anxiety has been so acute that she has been compelled to go to a hospital for mental disease. From time to time I have observed that anxiety does not seem to wear people down, and may even serve as a kind of protection against something which is regarded by the patient as more fearful. This case seems to be a verification of that postulate. Throughout a long, arduous life, both psychologically and from the standpoint of actual existence, for she has always been poor (she was on relief for a while, and I believe is still), she has been able to survive. The anxiety has probably been a protective factor in preserving her personality.

Spastic and Flaccid Hemiplegia of Cerebral Origin. Dr. Benjamin H. Balser.

A group of 38 cases of vascular hemiplegia of cerebral origin are presented; in 19 of these the motor paralysis was of the flaccid and in 19 of the spastic form. Clinical and postmortem studies are reviewed, and the following conclusions are drawn:

1. Flaccidity is not related to or determined by lesions in the basal ganglia. Pathologic changes within these structures occur as frequently in spastic as in flaccid paralysis. In 2 cases of flaccid paralysis lesions were limited to the cerebral cortex.

2. In all cases in which clinical tests could be made disturbance (cerebral) of sensation was invariably associated with flaccid hemiplegia and with wasting of the muscles. Pathologically, there was always involvement of the parietal cortex, the middle limb of the internal capsule or the thalamus or some combination of lesions within these structures. In 4 of the cases of spastic paralysis sensation was involved on the hemiplegic side. I believe that there must be some sensory implication for the production of flaccidity, but that spastic paralysis may occur in the presence of some sensory disturbance.

I offer this clinical and pathologic analysis of a group of cases in the endeavor to shed some light on the problem of what factor or factors determine flaccidity in hemiplegia. It would seem that implication of the motor extrapyramidal structures is not the final explanation.

DISCUSSION

Dr. Tracy J. Putnam: The concept of spasticity is one which is hard to maintain in a pure state. Obviously, if a patient keeps an arm in a rigid, flexed position and the attendant reflexes are hyperactive, the condition should be called spasticity. What, however, should the condition be called when the patient's extremities are not kept in any particular rigid position but the deep reflexes are hyperactive? This is a state which has long been regarded as spasticity, and not without some justification, because there is a difference only in degree between the hyperactivity of the stretch reflex which holds the arm in a flexed position and the lowered threshold of the reflexes, which is recognized as hyperreflexia.

It was long supposed that spasticity was evidence of involvement of the pyramidal tract, and the older investigations almost uniformly upheld this concept. Later studies, such as those of Bergmark, suggested that only certain types of cortical lesions produced flaccid hemiplegia and that under such circumstances a sensory defect was often present. More recently Fulton and members of his laboratory staff have demonstrated by experiments on animals that there is a distinct difference in the results of cortical extirpation, depending on which portion of the cortex is removed. Still more recently the pyramidal tract has been cut in the human being in the treatment of paralysis agitans. After this operation the affected extremities are found not to be rigid to palpation, but they do have extremely active tendon reflexes. There is definite hyperreflexia of the

type which most clinicians call spasticity. It is difficult to elicit an abnormal response to passive motion by palpation, but this is brought out by electromyographic records.

A further complication is the fact that one sees patients with diffuse lesions of the cord in which a type of rigidity, great response to passive motion and hyperactivity of the tendon reflexes are present. Moreover, in many cases the result of injury, especially of the pyramidal tract, and of other long descending tracts, is temporary flaccidity. In the phenomenon of spinal shock, as pointed out by Bastian, the more complete the interruption of the long descending tracts, the more profound are the flaccidity and the depression of the reflexes of the muscles affected. Furthermore, experience shows that in human beings, and presumably in animals, affected by flaccidity resulting from sudden interruption of long descending tracts, the general condition of the organism has a great influence on the end result. If any infection is present in the body the deep reflexes never return and the lower extremities are permanently flaccid, and it is only when infection is avoided and nutrition maintained that the reflex activity returns to the affected segments, so that one can speak of spasticity in the extremities involved. It seems to me that the factor of spinal shock, or pyramidal tract shock, is one which has not been sufficiently evaluated in this problem. Perhaps it has more to do with spasticity and flaccidity than meets the eye. It is obvious that lesions which involve both motor and sensory pathways are more extensive than those which involve motor pathways alone, and it is possible this is the reason that one is apt to see long-continuing flaccidity. The result of an acute cortical lesion is often flaccidity lasting for many days or weeks, and I think one should raise the question whether the cases which Dr. Balser reports in which the condition lasted for only a few weeks are properly classified as cases of flaccidity. I should, therefore, like to ask Dr. Balser whether the condition of the patient made any difference in the condition of the reflexes and, also, at what point he would draw a line between reflex hyperactivity and spasticity. I should like to ask, further, whether the factor of nutrition seemed to come into the final condition of his patients. He has shown one cannot simplify the problem to the point of saying it is this part of the cortex or that part of the basal ganglia which is the crucial factor in the production of flaccidity or spasticity, respectively.

Dr. Margaret Kennard, New Haven, Conn. (by invitation): I was glad to be asked by Dr. Balser to discuss his paper tonight, because in general his observations on human beings agree well with those on chimpanzees and monkeys which my colleagues and I have made in Dr. Fulton's laboratory at the Yale School of Medicine, to the effect that flaccid paralysis is apt to be concerned with sensory rather than with motor disturbances (Kennard, M. A., and Kessler, M. M.: *J. Neurophysiol.* **3**:248-257, 1940).

For the purpose of this discussion I am calling flaccidity a decreased and spasticity an increased response to passive manipulation. In the monkey and the chimpanzee we have made pure cortical ablations from various portions of the sensory and motor cortex. By parietal ablation, and by no other type, we have been able to produce flaccidity, or a diminished response to passive manipulation, which is permanent and which is the result of a rather small lesion, with little generalized effect. If the postcentral gyrus or the entire parietal area is removed from one hemisphere, the contralateral extremities show certain other changes which are indicative of the sensory loss, and, in addition, there is diminished resistance to passive manipulation. Immediately after operation the knee jerks are abolished, but within a short time they return and become increased as compared with the knee jerks on the normal side.

Ablation of the precentral cortex results in a diminished response to passive manipulation which is of much shorter duration, although, unless area 4-s, the strip area of Dr. Marion Hines (*Am. J. Physiol.* **116**:76, 1936), is also involved, true spasticity does not occur. The knee jerks become hyperactive sooner after ablation of area 4, and diminished resistance to passive manipulation is not maintained as it is after a postcentral lesion. Ablation of portions of the cortex further

rostrad, areas 4-s and 6, results in true spasticity. If the whole hemisphere is extirpated, there follows an increased response to passive manipulation, which does not occur immediately after operation but appears within a few days or weeks in monkeys and within a few weeks or months in chimpanzees. This lesion is comparable to the one Dr. Putnam mentioned—the lesion that produces something called shock, something which is temporarily a hyporesponse and is transformed into an increased response after a certain length of time.

We have made isolated lesions of the basal ganglia—the caudate nucleus or the putamen or both—and when such a lesion was not complicated by a cortical lesion, we have never been able to decide that there was any true change in the response to passive manipulation. But if the lesion of the basal ganglia is combined with a lesion of area 6 of the cortex, I am certain that an increased response to passive manipulation is present. We have never been able to find any indication that flaccidity results from a lesion of the basal ganglia combined with any cortical lesion. On the other hand, it happens that we have two or three times made a lesion of the mesial lemniscus, and this has resulted in a hyporesponse to passive manipulation. When a lesion is made in the thalamus, which has been done occasionally, and the results of which I am not as certain as I am of the lesions just mentioned, diminution in response to passive manipulation occurs. These are all related to lesions of the cortex or the afferent tracts, and not to the long descending tracts which Dr. Putnam mentioned.

The question whether or not spasticity is a heightened stretch reflex, an increase in a lengthening and shortening reaction, is one which merits discussion. In our monkeys, when the lesion is purely parietal and the response to passive manipulation is diminished, the knee jerks become increased. Since the tendon reflexes constitute a simple example of the stretch response, it is difficult to understand a diminished response to passive manipulation on the basis of the stretch reflex in the presence of a heightened knee jerk. We have tried to show that the increase in the knee jerk was only apparent, and we have compared the condition to that in which the superior cerebellar peduncle is cut. After this procedure there is also a flaccid extremity, but the knee jerk is only apparently, not truly, increased; it is a pendular knee jerk, which is of an entirely different type from that which follows a parietal lesion.

I do not think that Dr. Balser's statement of a segmental reflex will explain this, and I have never been able to find any one who would try to explain it. I should like to ask Dr. Balser whether he can throw any further light on the matter.

Dr. Abraham M. Rabiner: I was pleased to hear Dr. Kennard avoid the term "flaccidity" and substitute the designation "hyporesponse to the stretch reflex." Here with lesions of the pyramidal tract, the basal ganglia and the cortex, it is rather disconcerting to hear such loose terminology applied to the muscular state of the extremities. One should be meticulous in differentiating whether the patients present spasticity, with the increased response to the stretch reflex in the flexor or antigravity muscles only, or rigidity, with the increased response in both the agonistic and the antagonistic muscle groups. Rigidity one associates with an extrapyramidal and spasticity with a pyramidal pathologic process. I should also like to call attention to the inaccuracy of the term flaccidity when applied to the muscular status in hemiplegia without the degree of spasticity one ordinarily expects in such a condition. One often sees patients who do not show much spasticity, and such a state has often been described as flaccidity. Surely no one would think of regarding this condition as in any way comparable to the flaccidity seen in cases of lower motor neuron paralysis. There simply is not as much spasticity as is usually seen in hemiplegia. For many years those of us who have studied the problem of hemiplegia in hospitals for chronic disease have known that if there is not the ordinary degree of spasticity, we should expect some sensory changes, and this has been confirmed on examination. We have interpreted this observation as indicating a lesion of the postrolandic area, in addition to the motor involvement. Whenever we have found muscular atrophy in a case of hemiplegia we have demonstrated corresponding disturbances of sen-

sation. It is gratifying tonight to hear Dr. Balser present a clinicopathologic study and to hear Dr. Kennard discuss experimental results in primates that confirm the clinical opinions that we have maintained all these years.

DR. RICHARD BRICKNER: I have listened with interest to the paper and to the discussion, but still something bothers me. I am a little loath to abandon altogether the idea that the basal ganglia are connected with changes in tone under conditions of hemiplegia; it is certain, of course, that associated with many disturbances involving the basal ganglia there are changes, usually increases, in muscle tone. It seems to me a little sweeping to disregard such evidence, and I should like to ask a question. Dr. Balser showed cross sections of the basal ganglia and said there were no lesions in them; I wonder whether semiserial sections were made, so as to make sure the basal ganglia were really untouched. On the other hand, when lesions in the basal ganglia were seen, what was the condition of the rest of the ganglia? Might not enough have been preserved to function actively? These questions will have to be answered before it can be accepted that the outcome is the same whether the basal ganglia are involved or not.

DR. E. D. FRIEDMAN: May I add a word of emphasis to what Dr. Rabiner has just said? The great Oppenheim, speaking on the basis of years of experience, said that whenever in upper motor neuron disease there is absence of spasticity one should always look for simultaneous implication of the sensory pathways.

DR. BENJAMIN H. BALSER: I thank the discussants for their participation in this presentation. I shall consider the questions in order. But, first, I wish to point out that so much discussion about flaccidity and spasticity indicates that neurologists are pretty well acquainted clinically with these phenomena. One does observe the phenomenon of diminution of resistance in response to passive movement in some cases of hemiplegia of cerebral origin, and my presentation is limited to cases in which the origin is an insult to the cerebral hemisphere.

Dr. Putnam raised the question as to the duration of the paralysis in some of the cases, and rightly so. In 5 of the cases the paralysis was present for more than one year. The longest duration was four years and some months, and in these cases there was flaccidity as one thinks of it in the clinical sense, that is, diminution of resistance in response to passive movement. In 12 of 19 cases deep hyperreflexia existed in the presence of a flaccid type of paralysis, and the hyperreflexia did not seem to be related to the "tonal" status (I use the word "tonal" in quotes, employing it only in relation to flaccidity and spasticity). Dr. Kennard raised the question whether the segmental reflexes explained the hyperreflexia in the presence of flaccidity. That is the only explanation I can give at present.

As to Dr. Rabiner's question about flaccidity as it occurs with low motor neuron lesions, the deep reflexes are lost, but in many of the cases presented here the deep reflexes were hyperactive.

With respect to lesions in the basal ganglia, I did not prepare serial sections, but made only gross examinations of the basal ganglia. Varying degrees of involvement were observed, with complete disappearance of the basal ganglia structures in some cases, and I designated the changes as +, ++ and +++, on an arbitrary basis. One finds involvement of the basal ganglia as frequently in one situation as in the other—again emphasizing that it does not occur simply in cases of flaccid paralysis.

Visualization of the Brain and Spinal Cord with Diiodotyrosine-Gelatin Contrast Medum, Including Observations on the Fate of This Material. DR. HAROLD H. LEFFT (by invitation) and DR. J. ARTHUR MACLEAN JR. (by invitation).

Since the introduction of iodized oil as a contrast medium in roentgenography of the spinal cord, there have been many attempts to produce radiopaque and radioactive substances which could be injected into the subarachnoid system or the ventricles of the brain without causing any local or systemic damage to the

body. The deleterious effects of these particular compounds have been recognized and reported in the literature by many investigators.

The radiopaque compound under discussion here consists of powdered diiodotyrosine suspended in a solution of gelatin. Diiodotyrosine is an amino acid which contains 58 per cent iodine by molecular weight. It is normally found in the thyroid gland and structurally represents an intermediary product of thyroxin. The gelatin is a simple, nonantigenic protein which acts as the vehicle. To insure the same hydrogen ion concentration as that of blood plasma, a p_H of 7.4 is constantly maintained.

Inasmuch as this suspension of diiodotyrosine in gelatin is completely miscible with spinal fluid, it renders the spinal fluid radiopaque. The gelatin holds the diiodotyrosine in suspension, even after dilution by the spinal fluid, long enough for roentgenograms to be secured.

Being heavier than the spinal fluid, diiodotyrosine in gelatin will completely gravitate to the most dependent portions of the spinal canal or ventricles within a few hours after injection. It will remain there until the suspension of the diiodotyrosine in gelatin is broken up and all the constituents are absorbed.

Before this substance is injected into the subarachnoid space or the ventricles of the brain, it must be liquefied. At room temperature the material is in a solid or gelatinous state. The vial containing the contrast medium should be placed in a container of very warm water until liquefied. The vial should then be thoroughly shaken until the substance is homogeneously suspended. For injection into the subarachnoid space or the ventricles of the brain an 18 gage needle should be employed. The procedure of choice in taking myelograms or ventriculograms is to withdraw the same amount of spinal or ventricular fluid as is to be replaced by an equivalent amount of the contrast medium.

In our series the condition of the patient following the injection of diiodotyrosine in gelatin did not vary whether the material was injected intrathecally or intraventricularly. During the first few hours the patient usually rested quietly and registered no complaints. Occasionally a feeling of nausea or a vomiting spell would possess the patient, but these symptoms subsided quickly. More often the reactive type of patient would complain of headache. However, the headache was not as severe as when air was used, and with proper sedation and use of an analgesic the pain was generally controlled or arrested.

The average temperature after the taking of a myelogram was 101.5 F., while the average after the ventriculographic procedure was 102.3 F. These elevations of temperature usually occurred six to eight hours after injection and were not associated with any notable fluctuations of the pulse or respiratory rate. In fact, they were generally of short duration and frequently subsided within two to four hours after onset.

To investigate the absorption of this compound, routine determinations of iodine in the blood and urine were made in a series of 5 cases, in 4 of which a myelogram and in 1 of which a ventriculogram was taken. Daily specimens of urine were obtained in the same group of cases for a period of five days, and the iodine level of the total quantity which was excreted in each twenty-four hour period was determined. These observations revealed the gradual absorption of the diiodotyrosine from the subarachnoid or the ventricular system and the subsequent excretion of this compound by the kidneys within five to seven days.

To determine the intensity of the meningeal reaction following the injection of varying concentrations of diiodotyrosine in gelatin, a series of lumbar punctures were performed in a group of 8 cases, in 5 of which myelograms and in 3 of which ventriculograms were taken. These spinal punctures were made every twenty-four hours for seven days, and each specimen was sent to the bacteriologic laboratory for total and differential cell counts. The highest cell counts were observed at the twenty-fourth hour. The spinal fluid in this seven day period was usually turbulent and opalescent. However, it gradually cleared during the

period, until the normal colorless state was resumed. As the spinal fluid cleared, the cell count progressively diminished until the seventh day, when the cytologic content was usually normal.

Our clinical experience in 44 cases in which this new compound was used as the contrast medium, in 30 of which myelograms and in 14 of which ventriculograms were taken, proved to us that diiodotyrosine in gelatin is a valuable aid in the visualization of the brain and spinal cord. There was not a single death in the entire series which could be attributed to the use of this material. Moreover, the patients did not present the pathologic symptoms which so frequently follow the injection of other contrast mediums. Follow-up examinations made in the majority of cases over a period of several months failed to reveal any clinical manifestations of pathologic changes in the central nervous system.

DISCUSSION

DR. TRACY J. PUTNAM: Dr. Lefft has brought good news indeed. I am only sorry he was too modest to mention the fact that he not only originated the idea of using diiodotyrosine in gelatin, but personally prepared the solution in sterile form for use—a pharmaceutic procedure of no small difficulty.

No one here needs to be told of the value of ventriculography and myelography. Their dangers are also well known. There have been many attempts to find some innocuous material for contrast purposes. Few of these attempts have reached the literature. I have known of a good many of them, and in general they have been unsuccessful. Dr. Lefft, again, was too modest to tell how he arrived at the conception of the use of a diiodotyrosine-gelatin medium, and I hope he will not fail to do so in his closing comments, for the growth of any such concept carries lessons of its own. To my mind the significant thing is that diiodotyrosine in gelatin is an almost insoluble material which can be prepared in very small particles. Its insolubility probably accounts for its relatively slight effect on the arachnoid membrane and the ependyma, and the smallness of its particles probably explains the fact that they can be deposited relatively easily. The reaction which Dr. Lefft has demonstrated (I have had the pleasure of looking over his series of slides, and those he showed tonight are representative) is of short duration. It is rather violent as long as it lasts; indeed, it is my impression it is more severe than the immediate histologic reaction which follows the injection of iodized oil or of air. It is rather unusual to find cell counts as high as these within the first twenty-four hours after the injection of air or iodized oil. However, Dr. Lefft has given convincing evidence of the long term innocuousness of his material. I should prefer to see it withdrawn from the spinal canal after the myelographic procedure, and I suppose that would be feasible. Has Dr. Lefft attempted to withdraw the material, as has been suggested in the case of iodized oil and of thorium dioxide?

DR. LEO M. DAVIDOFF: There are three essential qualities of a contrast medium: the degree of radiopacity, the immediate reaction of the patient to the introduction of the medium and the final, or long term, effect of the material—its absorbability and its final elimination from the body. The radiopacity was evident in the beautiful slides that Dr. Lefft threw on the screen. As to the immediate reaction, when there is pleocytosis, with a count as high as 16,000, the immediate reaction can be said to be relatively severe. It is true that this happened in the experimental stage of the use of this material and with lower concentrations and smaller quantities the cellular reaction has been reduced, but it is still rather high as compared with that to gas. I believe I have seen as high as 400 cells per cubic millimeter of spinal fluid after the use of air or oxygen, but have never seen or heard of the count being higher. As Dr. Putnam has suggested, the product, while it has many fine qualities, can still be improved, and I am sure the authors of the paper will try to improve it in this respect.

I believe that the advance has been greatest with respect to the long term effect and the final absorbability of this substance. The fact that only a trace of the material can be found three or four days after injection makes its discovery a great step in advance.

To go back to the second quality of the medium, the immediate effect on the patient, I had the opportunity of seeing a patient, the young woman whose roentgenograms were thrown on the screen, about three days after the material was injected. She was still uncomfortable. Her lesion produced some root pains, which had been increased by the use of the medium, and this increased pain was still present. She looked rather seedy; she was nauseated and had a rash on her chest and back, some headache and a slight degree of fever. Roentgenograms taken at the hospital with which I am associated three days after the material was injected no longer showed any evidence of opaque substance in the spinal canal. Within a few days her systemic symptoms entirely disappeared, and five days after she was admitted to the hospital her rash had disappeared and she was well, except for her original complaint. We considered her a good operative risk at that time.

I think the fact that the material is absorbed, and within as relatively short a period as five or six days, makes it possible to eliminate the procedure of the removal of the material. That it can be left in without danger, although Dr. Putnam does not agree with this, makes it advisable to do so. The removal of iodized poppyseed oil, even as it is done nowadays, is undesirable; formerly a small laminectomy was necessary, which made it a major procedure. Mixter has shown the oil can be removed immediately after the roentgenograms are taken, and in so doing the removal of the material is relatively easy, but it still means a period under the fluoroscopic screen, with exposure of the patient and the operator to roentgen rays, the accumulated effect of which is not desirable. With regard to thorium dioxide, I believe the accepted method of removal is by spinal drainage, which is also undesirable. I sincerely hope this work will continue, but I believe it has already reached a stage at which, if the material were available, I should not hesitate to use it with my patients.

Dr. J. Arthur MacLean: I had the privilege of operating in all but 2 of the cases in which the material was injected; those were the cases in which Dr. Davidoff operated. Laminectomy was done anywhere from forty-eight hours to twelve days after the material was injected, and after the first few days there was no gross evidence, on examining the cauda equina, the roots or the spinal cord, of any tissue reaction. This is in contrast to the appearance after the injection of iodized poppyseed oil, after it has been allowed to remain for several days, when definite evidence of irritation of the nerve roots is observed. In the cases of brain tumor there was no evidence of any reaction of cortical tissue. In cases of brain tumor in which operation was performed immediately after the material was injected there was less symptomatic and thermal reaction than when the patient was allowed to lie in bed for a few days after the injection. Dr. Lefft has painted the lugubrious side of these reactions. It is essential that the poor reactions be emphasized, but I should say that the majority of patients did not have such reactions. We had a case of brain tumor in which we did a ventriculogram in the morning under local anesthesia, and presented the patient at the neurologic conference in the afternoon. In none of our cases in which myelograms were taken was any general anesthetic given, and in none except the first 5 or 6 cases did any sensation follow injection of the material. In these early cases the material differed in its preparation, and there was considerable pain for a few minutes. When we removed the small amount of glycerin which was in the first preparation the pain was eliminated. Nor did the patient have any pain on changing position with the material in place. In certain conditions smaller amounts of the material are required than in those presented, for instance, in the treatment of protruding intervertebral disk, which is prevalent now and in which partial obstruction, or simply encroachment on the dural canal, is present. Iodized

poppyseed oil is not of value unless enough can be introduced to fill completely the canal above that encroachment, and if there proves to be no such encroachment the oil must be removed. This is one of the important reasons for work on absorbable radiopaque material.

The reaction seems to be dependent on the amount of material injected. We had children and babies in this series. The case of meningocele was presented because the child was a poor risk, with multiple congenital defects. This case was one of the early ones, and we felt there was nothing to lose; fortunately, there were no ill effects. Some deaths have been associated with this study, mainly in the early part of the series. We had a patient with what was suspected clinically to be tuberculous arachnoiditis. Cisternal puncture was attempted. His condition was poor. The material was introduced; roentgenograms were taken, and a diagnosis was established. Four days later he died. Autopsy revealed the arachnoiditis, which was not as extensive as was thought clinically and, in addition, a small tumor at the foramen magnum. The point I want to make is that his condition was critical, and yet injection of the material, in spite of the febrile reaction, was not directly responsible for his death. In another case, that of a brain tumor, death resulted from secondary hemorrhage, thirty hours after the injection. The microscopic reaction was no more severe than one would expect from an epidural hemorrhage. In those cases in which death occurred we were not able to attribute any of the pathologic changes to the material used.

Dr. Harold H. Lefft: Dr. Putnam puts me to task when he asks how diiodotyrosine in gelatin was discovered. About ten months ago I was doing some experimental work on decerebrate rigidity with "curare in gelatin" when Dr. MacLean suggested that I temporarily drop this problem and try my hand at finding a nontoxic and absorbable contrast medium for visualization of the spinal cord and brain. Any substance which was to be injected into the subarachnoid or ventricular system, I thought, ought to be compatible with body tissues. In fact, such a substance could perhaps be found in the human body itself. With this reasoning to guide me, I investigated all the compounds containing iodine which normally occur in the human body. This led to the consideration of three such substances, all of which were constituents of the thyroid glands. The first was thyroxin, which was not to be considered because of its toxicity in the huge quantities which had to be employed. The other two compounds, monoiodotyrosine and diiodotyrosine, were intermediary products of thyroxin. However, they were physiologically inactive.

Diiodotyrosine was chosen because of its greater iodine content and relative stability. This substance proved to be the radiopaque factor. However, a suitable vehicle in which this relatively insoluble compound could be suspended had to be found. While holding a vial of "curare in gelatin" in my hand one day, I observed the gelatin liquefying. On tipping the vial this substance flowed like an oil. This property led me to mixing some diiodotyrosine in gelatin, with the result that a homogeneous suspension of the two substances was obtained. This new material could be easily injected through an 18 gage needle, and it was subsequently used in all of the experimental procedures.

In answer to Dr. Putnam's comment regarding the intensity of reactions to air as compared with those to diiodotyrosine in gelatin, I have never done any experimental work along these lines. From a pathologic viewpoint such an experiment would be interesting.

The withdrawal of this contrast material after injection can be easily accomplished by the ordinary drainage methods. In view of the fact that diiodotyrosine in gelatin is absorbable, we have not attempted drainage in our cases.

In regard to Dr. Davidoff's comment about the 16,000 cell count in the spinal fluid, in that case a solution containing 2.5 Gm. of diiodotyrosine was injected. At present only one third of that quantity is injected intrathecally, and the cell counts probably range between 5,000 and 7,000 per cubic millimeter.

The only case in which a cutaneous rash developed, as I mentioned in the paper, was that seen by Dr. Davidoff.

CHICAGO NEUROLOGICAL SOCIETY

DR. ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, Jan. 15, 1942

Hemangioblastomas of the Meninges and Their Relation to Lindau's Disease. DR. HOWARD ZEITLIN.

Lindau pointed out the hemangiomatous nature of certain cystic tumors of the cerebellum. He showed that these tumors are frequently associated with so-called angiomas of the retina (von Hippel's disease), brain stem and spinal cord and pointed out the concomitant occurrence of cystic tumors in the somatic organs, such as the pancreas, kidneys, adrenal glands and liver. This pathoanatomic complex, the chief feature of which is a hemangioblastoma involving the cerebellum, is known as Lindau's disease.

The histologic structures of 2 tumors have been studied: one, a typical hemangioblastoma of the cerebellum (Lindau's tumor); the second, a hemangioblastomatous tumor arising from the meninges over the cerebral hemisphere. Both tumors were composed of numerous capillary blood vessels and intervascular epithelioid cells. The intervascular cells seemed to be intimately connected with the outer coat of the capillary wall, from which they appeared to originate. These cells were fairly large and contained a centrally placed nucleus and ample cytoplasm. Numerous small vacuole formations filled with lipoid material gave the cells the appearance of "foam" cells. Examination of sudan III–stained sections with polarized light disclosed dense masses of doubly refractile bodies, many of which showed typical Maltese figures. Sections stained by Perdrau's method revealed reticulin fibers limited to the areas about the walls of blood vessels.

I conclude that the hemangioblastomas of the meninges form a distinct pathologic entity and are identical in structure with the hemangioblastomas of the cerebellum (Lindau's disease). Lindau tumors arising within the central nervous system should, therefore, be classified as hemangioblastomas of the meninges. Although Lindau tumors are most prevalent in the hindbrain (cerebellum, pons, bulb and spinal cord), other areas of the brain are not immune.

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DISCUSSION

DR. ARTHUR WEIL: The impression I gained from the literature is that Lindau's disease is that peculiar combination of hemangioblastoma of the cerebellum, hemangioblastoma of the retina and cysts of the pancreas and kidneys, and perhaps other tumors. Olivecrona spoke of the Lindau tumor, referring to the isolated cerebellar hemangioblastoma. In justice to others, however, one should point out that this tumor was described before Lindau and that Berblinger even claimed priority for having described the syndrome in 1922, before Lindau's publication in 1927.

DR. PAUL BUCY: I heartily agree with Dr. Zeitlin's thesis that all hemangioblastic tumors are meningeal in origin. The term hemangioblastoma of the cerebellum obviously refers to the location of the tumor; it does not arise from neural tissue. As Dr. Zeitlin pointed out, the cerebellar hemangioblastoma is frequently associated with similar tumors in the spinal cord. Several years ago, in reviewing the literature, Dr. Paul M. Levin found that in each case of cerebellar hemangioblastoma in which a complete autopsy was performed a hemangioblastoma of the spinal cord was also present.

I should like to put on record an interesting example of this disease. In 1928 Dr. Bailey and I operated on a young woman for a cystic hemangioblastoma of the cerebellum. She made a gratifying recovery, but in 1935 symptoms of compression of the spinal cord appeared and a laminectomy was performed. A heman-

gioma of the spinal cord was revealed, which could not be removed. A decompression was made; she was given roentgen therapy, and she again recovered. Recently her 15 year old son had a hemangioblastoma of the cerebellum removed. This illustrates the hereditary character of this tumor, as well as the frequent involvement of the spinal cord.

Histopathologic Features of North Dakota Type of Epidemic Encephalitis. Dr. Arthur Weil and Dr. Paul J. Breslich.

Epidemic encephalitis has been observed in the United States at different times since the end of the first World War. In the East (New York and Massachusetts) and in the West (California) minor epidemics occurred between 1921 and 1926. In the Middle West an outbreak of major proportions was reported in St. Louis in 1933 and 1937, which also affected the neighboring states of Illinois and Kansas.

The fact that a similar type of encephalitis is present in horses both on the Atlantic seacoast and in the Western Pacific states, and that immunologically the virus in the disease in horses is found to be identical with that in cases of the human epidemic occurring in the same neighborhood led to the recognition of the equine type of encephalomyelitis in man. This type, too, occurs in epidemic form; a minor epidemic was reported in children (1938) in Massachusetts and two major epidemics in North Dakota in 1938 and 1941. All these different types, in common with the Japanese B type, show the highest seasonal incidence during August and September.

The present investigation is concerned chiefly with a histopathologic comparison of the St. Louis type of epidemic encephalitis, the equine type and the equine type of encephalomyelitis in man. All these forms have in common a characteristic inflammatory reaction and a characteristic distribution of the foci of inflammation. The inflammatory reaction consists of perivascular monocytic exudate and an intense glial proliferation, with the formation of dense foci of glia and diffuse hyperplasia and hypertrophy of the astroglia. The inflammatory reaction is most intense in the gray masses of the midbrain and gradually decreases in intensity both rostrally and caudally. In the cortex the white matter also is involved; the meningitis parallels in intensity the encephalitis of the underlying brain tissue.

It appears that both the Massachusetts and the North Dakota equine type of encephalomyelitis in man differ from the St. Louis type of epidemic encephalitis in the presence of large foci of necrosis, especially within the white matter, which develop from severe perivascular edema, observed in the early stage. These foci contain proliferated glia cells transformed into scavenger cells and the debris of both myelin sheaths and axis-cylinders. While in the St. Louis epidemic small cocci (secondary invaders, superimposed on the virus invasion[?]) could be detected within the perivascular exudate in the majority of cases, such organisms were absent in the North Dakota epidemic. In 1 case only tiny diplococcus-like structures, measuring less than 500 millimicrons, were seen in the perivascular exudate.

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DISCUSSION

Dr. George B. Hassin: I did not intend to discuss Dr. Weil's paper, as I have no personal experience with the North Dakota type of epidemic encephalitis. From what I saw this evening, I understand that the changes are practically the same as those one sees in any other form of encephalitis. There are perivascular infiltrations, formation of nodules and, in some cases of the severe form, foci of degeneration or softening. The intensity and extent of the lesions impressed me as being greater in Dr. Weil's case than they are in the ordinary type of lethargic encephalitis. The cortex seems to be more often affected in the St. Louis type of epidemic encephalitis than it is in the lethargic type. I do not think anybody

could make a diagnosis of a definite type of encephalitis under the microscope, and I wonder therefore whether Dr. Weil could diagnose a case of the North Dakota type without knowing the clinical features of the case, the area of the brain from which the section came and the parts of the brain involved, that is, the localization of the lesions in general.

I think Spatz was the first to make extensive studies of the localization of the lesions in various types of encephalitis by staining sections from the whole brain. It was thus easy for him to demonstrate which parts of the brain were preferably involved in each type of encephalitis. The midbrain was found to be affected in every type of encephalitis which he studied.

Dr. Richard B. Richter: I have had no experience with human material of the equine type of encephalitis and very little with that of the St. Louis type. I can say, however, that the histopathologic changes as they occur in experimental animals show the same general tendencies that Dr. Weil pointed out, namely, greater acuteness of inflammatory response and more severe necrosis in equine encephalitis than in the St. Louis variety. However, the intensity of the reaction to both viruses varies greatly from animal to animal, even in the same species. Some mice, for instance, infected with the St. Louis virus exhibit a reaction in the brain so intense that it resembles that seen in the same animal when inoculated with the equine virus, and cannot be distinguished from it. On the whole, I cannot say that it is possible pathologically to distinguish one virus infection from another in animal material with any degree of certainty.

Dr. Joseph Luhan: I should like to ask whether Dr. Weil considers this form of encephalitis to be polioencephalitis, in contradistinction to leukoencephalitis. Did he have an opportunity to examine the motor areas of the brain in cases of North Dakota epidemic encephalitis? In a few cases of human poliomyelitis at Cook County Hospital in which autopsy was performed and in animals with poliomyelitis, I observed in every instance tissue foci in the cortex, limited almost exclusively to area 4. This may be a differentiating point in the pathologic diagnosis of poliomyelitis and these types of virus encephalitis. I had believed, as Dr. Hassin pointed out, that these types of encephalitis cannot usually be differentiated histopathologically, except for intensity and localization (sites of predilection) of the disease process.

Dr. Reuben M. Strong: Have there been any studies on the effects of encephalomyelitis on mosquitoes?

Dr. Paul Bucy: Was Dr. Weil not surprised to observe such an intense astrocytic reaction with a disease process which had been present only three to five days?

Dr. Roy R. Grinker: Dr. Weil clearly demonstrated the histopathologic syndrome of virus diseases that attack the central nervous system. At one time there was considerable opposition to Spielmeyer's thesis that the reaction to the presence of a virus infection is stereotyped. Would the absence of the characteristics that Dr. Weil has so well portrayed lead to negative conclusions, namely, that the disease is not a virus infection? I refer to a number of conditions still termed encephalitis or, more conservatively, encephalopathy, in which only the parenchyma is affected and the inflammatory reaction is minimal or absent. Would Dr. Weil believe they were not virus diseases?

Dr. Arthur Weil: I am somewhat surprised at some of the statements in the discussion. Dr. Hassin said it was impossible to differentiate "any type" of encephalitis and that the inflammatory reaction of the brain was always the same. Has he ever seen in a case of proved bacterial infection of the brain, such as that due to Pneumococcus, Streptococcus or Bacterium coli, the particular reaction which I have demonstrated tonight in a case of epidemic virus encephalitis? In all my experience I have never seen this particular combination of mesenchymal and glial defense reaction in a case of bacterial meningoencephalitis or of embolic disseminated encephalitis.

As to the reaction of laboratory animals to virus infection which Dr. Richter discussed, Dr. Luhan, who has done work with the poliomyelitis virus in animals in our laboratory, can confirm the observation that shortly after the inoculation of the virus the peculiar combination of glia foci and perivascular lymphocytic infiltration could be demonstrated in the brain stem. Dr. Richter confirmed my statement that in the equine type of epidemic encephalitis the intensity of the inflammatory reaction and tissue necrosis is more severe than in the St. Louis type of epidemic encephalitis. Of course, there are individual differences in the defense mechanism of the different brains, but they apply to the degree of intensity only, not to the general type of the histopathologic picture.

Dr. Luhan's question whether one should classify the North Dakota type as polioencephalitis or leukoencephalitis cannot be answered definitely in one way or the other. Both the gray and the white matter are affected alike. But, in contradistinction to the St. Louis epidemic, in which the cortical gray matter and the nuclei of the brain stem were more affected than the white matter, in the present epidemic the white matter was also severely involved. I cannot answer his question whether the localization of the inflammatory reaction in poliomyelitis to area 4 of the motor cortex could be a differential sign.

As to the problem of transmission which Dr. Strong mentioned, the reports are at present contradictory. It has been stated that the virus was discovered in the brains of prairie chickens. The poliomyelitis virus has been demonstrated in flies. There is the fact that in both the St. Louis and the North Dakota epidemics more cases were reported in rural districts than in the great cities. Such a topographic distribution may point to transmission by insects.

With regard to Dr. Bucy's question, I wish to point out that the glial reaction which was demonstrated occurred in a patient who survived for ten days. However, after what has been learned from experimental evidence, one should expect intense astrogliosis not only as a chronic reaction but within a few days of experimental intoxication, for example, that resulting from metrazol.

I can hardly answer Dr. Grinker's question positively. From my experience, however, I may say that if the characteristic combination of glial and mesenchymal reaction is absent, one is not justified in assuming that one is dealing with an isolated case of the virus-borne epidemic type of encephalitis. I refer to the publication of Adler, who studied the histopathologic changes in a great number of cases in which a clinical diagnosis of encephalitis had been made; from one of these she selected the brain, which showed the typical picture of the equine type of encephalitis.

Dr. George B. Hassin: I did not mention cerebral reactions to virus infections, but simply emphasized that in any type of acute encephalitis, whatever the name, there are the same general pathologic features. In the case Dr. Weil demonstrated tonight foci of what he called necrosis were prominent. Such areas, which I should call foci of degeneration or softening, may be seen in any type of severe infectious encephalitis—herpetic encephalitis, for instance—while nodules in combination with perivascular infiltrations may be a prominent feature in trichinosis encephalitis, and even in the lethargic form if the infection is severe.

Mesencephalic Tractotomy: A Method for the Relief of Unilateral Intractable Pain. Dr. A. Earl Walker.

Although many neurosurgical procedures have been suggested for the treatment of intractable pain, chordotomy is still the most satisfactory method for the relief of pain in the lower extremities, abdomen and thorax. It is not a safe procedure when carried out in the upper cervical segments, owing to the danger of respiratory failure. To avoid such a complication Dogliotti has suggested section of the lateral lemniscus in the rostral part of the pons.

From neuroanatomic studies on the spinothalamic and secondary trigeminal pathways, it appears that an equally effective and simpler section of the entire pain fibers from one half of the body, including the face, may be carried out in

the mesencephalon. The site of section is reached by elevation of the temporo-occipital lobe and incision of the tentorium to the incisura. The section is made from the lateral sulcus of the mesencephalon superiorly across the brachium of the inferior colliculus, the incision being 5 mm. in depth. This procedure was carried out on 3 patients suffering from intractable pain. In each case relief of pain was immediate and persisted for the life of the patient. After operation the patient had a mild feeling of numbness in the upper extremity and complete hemianalgesia and hemithermanesthesia. There was no ataxia and no evidence of oculomotor paresis. Proprioceptive sensibility was intact. The patient was able to walk normally.

A differential section was attempted in 1 case, but the result was not satisfactory. Analgesia limited to the upper extremity and the face was present for a short time after the operation, but appreciation of pinprick returned in two or three weeks.

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DISCUSSION

DR. BENJAMIN BOSHES: I wonder whether this procedure would stop such pain as that of postherpetic neuralgia, in which the sympathetic as well as the somatic fibers appear to be implicated.

DR. L. M. WEINBERGER: This is a beautiful contribution to surgery of the brain stem. It unquestionably offers advantages unequaled by any other available procedure. I should like to ask three questions: First, what have been the mortality and morbidity rates for this procedure? Second, have the patients subjected to this operation complained of any unpleasant sensations in the analgesic area? Third, has section of the trigeminal pathways produced the "onion skin" type of analgesia in the face?

In experiences with Sjöqvist it was found that the sensory disturbance of the face within the distribution of the descending trigeminal path was in terms of the peripheral division. Because of this observation, it was suspected that the "onion skin" distribution noted in cases of syringobulbia was a result of injury to the secondary trigeminal fibers; for this reason I am interested in the results of examination of the faces of the patients in whom the secondary trigeminal fibers were cut.

DR. ROY R. GRINKER: I noticed that much of the moving picture was given to proving that the patient had accurate tactile localization, and I wondered about the reason for that.

DR. A. EARL WALKER: I cannot answer the question regarding the effectiveness of the procedure in treatment of postherpetic neuralgia, since none of the 3 patients suffered from that disorder. I presume, however, on the basis of the results of chordotomy in this disease, that mesencephalic tractotomy would be equally effective.

The difficulties encountered at operation varied greatly. In the first patient considerable bleeding occurred at the time of section and was controlled only with difficulty. This hemorrhage undoubtedly contributed to the death of the patient two days after operation. The other 2 patients died of the primary disease, one and two months after operation, respectively. Neither presented neurologic complications. One of them had a carcinoma of the tongue with metastasis to the cervical lymph nodes. Although she was 57 years old and had complete ankylosis of the jaw, she had no postoperative complications.

These patients had stated that the contralateral arm and leg felt rather cold and numb, but this did not appear to cause them any concern, for they did not comment on it unless questioned.

The analgesia and thermanesthesia were complete over the entire face, and none of the patients presented the "onion skin" type of sensory disturbance.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

RAYMOND W. WAGGONER, M.D., *President, in the Chair*

Regular Meeting, Jan. 15, 1942

Malarial Therapy at the Pontiac State Hospital: A Review of Fifteen Years' Experience. DR. J. A. VATZ, Pontiac, Mich.

Malarial therapy was administered to 253 patients with dementia paralytica at the Pontiac State Hospital between 1926 and 1941. From a study of their cases certain conclusions are reached. The best results were obtained from a combination of pyretotherapy and chemotherapy. Patients to whom malarial therapy could not be administered and who received only chemotherapy showed uniformly poor results. The highest percentage of remissions occurred in patients between the ages of 20 and 39. The mortality rate associated with malarial therapy increased with age. The average death rate was 5.07 per cent. All patients who were paroled or classified as improved showed evidence of improvement within six months after the malarial therapy. The prognosis for remission was slightly higher in persons who did not give a history of alcoholism than in those who did.

A Study on Senile Dementia. DR. A. N. SCHNEIDER, Pontiac, Mich.

The case records of 50 consecutive patients over 60 years of age who were admitted to the Pontiac State Hospital for the first time between Oct. 11, 1938 and March 22, 1940 are reviewed. Analysis of these cases reveals that by June 1, 1941, 28 of the patients had died, 5 had been discharged, 2 were improved but were still in the hospital and 15 were unimproved. Postmortem examinations of 14 of the 28 patients who died showed evidence of deteriorating organic disease of the brain in 12. The outstanding manifestations in the 15 unimproved patients were impairment of memory, delusions, disorientation and untidiness. Three patients had manic manifestations, and 2 had symptoms of depression associated with the senile changes. In 11 of these patients there were somatic disturbances which undoubtedly interfered with mental improvement.

In spite of the fact that these patients were treated according to the principles of psychiatry and internal medicine, only 8 per cent showed definite improvement, and an additional 4 per cent exhibited slight improvement.

Indications and Contraindications to Encephalographic, Ventriculographic and Cerebral Angiographic Examinations. DR. CARL F. LIST, Ann Arbor, Mich.

Encephalographic, ventriculographic and cerebral angiographic procedures are diagnostic methods which make possible the visualization of intracranial lesions by the introduction of roentgenographic contrast mediums. These procedures should be used only to supplement the clinical examination. The encephalographic and ventriculographic methods have been generally employed, and their accomplishments and limitations are well known. The comparatively small experience with cerebral angiography does not permit one as yet to state its indications with finality.

Encephalography makes possible the visualization of the cerebral ventricles and subarachnoid system by introduction of a gaseous contrast medium into the spinal canal. It is the only method which adequately demonstrates the subarachnoid space. A considerable percentage of encephalograms are technically imperfect, sometimes owing to obstructive lesions, sometimes without evident gross anatomic cause. The encephalographic examination is performed with ease but causes greater discomfort to the patient than the ventriculographic or the angiographic procedure. Encephalography is strictly contraindicated in conditions of increased intracranial pressure and is inadvisable in cases of suspected tumor of the brain

without signs of increased intracranial pressure. In all these cases the method not only fails frequently to give satisfactory diagnostic information but is highly dangerous. Encephalography is indicated and safe in a variety of neurologic conditions, such as developmental lesions of the brain (except for obstructive hydrocephalus and the Arnold-Chiari deformity), traumatic encephalopathies (excluding subdural hematoma), convulsive disorders, degenerative, atrophic and postinflammatory lesions and, in selected cases, vascular intracranial disease.

Ventriculography accomplishes exclusive visualization of cerebral ventricles by direct introduction of a gaseous contrast medium, preferably oxygen. The procedure requires complete neurosurgical equipment and should never be undertaken unless one is fully prepared to carry out a major intracranial operation. The dangers of the method lie in the possibility of intracranial hemorrhage or edema caused by the puncture or in secondary rise of intracranial pressure, a peril which can be lessened by retapping the ventricle or by immediate craniotomy. Ventriculography is indicated in conditions of increased intracranial pressure and is advisable in cases of suspected tumor of the brain without increased intracranial pressure because of greater safety and diagnostic reliability. Ventriculography is indispensable in the diagnosis of brain tumor, especially intraventricular tumor, which cannot be localized by the usual clinical methods. In cases of neoplasms of the cerebral hemispheres associated with high intracranial pressure the method is not always satisfactory or safe.

Cerebral angiography affords visualization of the intracranial blood vessels by injection of a contrast medium into the carotid artery. In a first phase, the terminal branches of the internal carotid are shown, and in a second phase, the cerebral veins and sinuses. The method is technically complicated, requiring operative exposure of the internal or the common carotid artery and perfect cooperation between neurosurgeon and roentgenologist. At present, thorium dioxide is the most satisfactory contrast medium available, and it appears to be innocuous if used in small quantity. Angiography is specifically indicated for the diagnosis of vascular lesions, such as intracranial aneurysm and arteriovenous malformation and in certain cases of arterial obstruction. It is also indicated in cases of lateralized tumors of the cerebral hemispheres, especially of the temporal lobe. While angiography is not superior to ventriculography as far as localization is concerned, it is a safer method to use in the diagnosis of hemispheral tumors with high intracranial pressure. Another advantage of angiography lies in the fact that it may demonstrate the characteristic vascular pattern of the tumor and thus permit an anatomic differential diagnosis (e. g., glioblastoma, meningioma, cyst).